ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 187 1968

THE DEVELOPMENT OF CHILDREN IN A SWEDISH URBAN COMMUNITY
A PROSPECTIVE LONGITUDINAL STUDY

I–VI

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To Arvid Wallgren

Preface

The six papers[1] in this supplement are the first collected results of a longitudinal study of the biological growth of children, somatic as well as mental development.

The study is part of an international coordinated investigation organized by the Centre International de l'Enfance in Paris. The Swedish study was started in 1954 at the Paediatric Clinic, Karolinska sjukhuset, where it is still in progress.

Professor Arvid Wallgren was the initiator of the Swedish study and has since the start inspired and encouraged the members of the Growth team and supported them in every way. After Professor Wallgren's retirement the team has been able to continue the study with the support and assistance of Professor John Lind.

The study was financially facilitated by grants from
Centre International de l'Enfance
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1 I, II, IV and VI submitted for publication in 1964, III in 1963.

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children of different ages, in a variable such as height or intelligence scores will throw no light on the course of growth in individual children It is highly misleading to think in terms of the height of the average child at each age and connecting these points, to assume that this mythical child could grow in this way The average not only conceals irregularities of growth rates in individual children, but may also conceal or greatly distort common trends such as the adolescent spurt when these occur at different ages in different children

In the United States the great value of longitudinal investigations was recognized at an early stage among others by Bayley [2] Dearborn & Rothney [7] Jones [18] MacFarlane [24] Shuttleworth [42] Sontag [44] Stuart [56 57] and Washburn [60]

The present investigation forms a link in international studies on the development of children co-ordinated by the International Children s Centre (I C C.) in Paris Those studies, listed in the order in which they were started are in progress in London, Paris Zürich and Brussels in Europe, in Dakar and Kampala in Africa and in Louisville in the United States An account of this internationally co-ordinated study with regard to its aims design and methods has been given in volume V of Modern Problems in Pediatrics with Frank Falkner as co-ordinator and editor and with contributions from team members in the different centres [13]

The general aim of these studies has been formulated as follows [16]

Within each country

(i) To chart the course of physical and psychological development of children, in terms of a number of important variables. (ii) To obtain reasonably comprehensive life histories, which will be applicable to a considerable variety of problems. (iii) To employ a sufficiently large sample to permit of statistical analysis (iv) To relate important features of development to other important variables, as, for example social background size of family parental methods, health etc (v) To study the inter relationship of one feature of development with another as, for example of physique and health behaviour problems and previous experience intelligence and physical health or of physique and behaviour

Between countries

(i) To determine to what extent the developmental process, and inter relationships between variables, show similar or different features in different countries. (ii) Where clear differences exist to attempt to explore the possible reason for them.

Owing to the intimate interrelationship between physical and psychological factors an adequate study of growth and development must include coordinated examinations and observations by various specialists A broad approach is essential. By repeated physical examinations and various body measurements and through simultaneous comprehensive psychological interviews and tests, as well as by an appraisal of social environment a picture of the total child in its environment may be attained An impairment of a child s physical health readily affects his general behaviour and conversely mental stress may cause marked changes in bodily functions

The aim of the Swedish investigation is to study children in a Swedish urban community in the Stockholm region according to the above mentioned principles Our primary main objects are

The physical investigations should be so designed as to give a broader picture of the growth of normal children than is available at present in Sweden. This can be achieved owing to the increased number of body measurements that are taken and to the longitudinal approach adopted for the evaluation of the growth process as such. Special emphasis is focused on increments for various age periods. Our purpose is to develop also a more detailed method of evaluating skeletal maturation from a smaller number of X-ray examinations than are made at present in Sweden.

The primary aim of the psychological investigations is the elucidation of those point which physicians teachers psychologists, parents and other persons who have to deal with children every day are compelled to take into consideration. There re for example the variation in sleep sleep disorders and sleep requirement time for cleanliness and toilet training eating habits and eating problems jealousy of siblings, different forms of fears et Our knowledge is very limited with regard to the variation in children behaviour att tudes and emotional reactions. Furthermore in the psychological investigations we endeavour to get a picture of emotional and int llectual maturation and the development of the child personality i his interaction with the other members of his f mily In connection with this are interested in studying the identification process and the child s adaptation to society and its value norms. In Sweden, however there is a shortage of standardized and well validated personality tests, especially for mall children. Experience gained with a battery of such techniques will increase the possibilities of evaluating personality development in children.

It is hoped that the present investigation may contribute to the discussion on the distribution of the intellectual, testable ability levels in different social groups. By testing children from infancy up through the years when the influence of the cultural environment probably becomes stronger the investigation may furnish information regarding possible shifts in the level of ability

This study may also assist in elucidating whether it is possible to predict at an early stage a child s vulnerability In the first place, we have in mind those children who are highly sensitive

We may summarize by stating that the main purpose of this investigation is to widen the knowledge on which preventive child care and the clinical judgement of children are based, and to attain a more profound and detailed insight into the mechanisms that guide the growth and development of children.

The organization of the Swedish study The Swedish study initiated by Arvid Wallgren, began to be planned in the autumn of 1954 after two of us (P K. and G K.) had had the opportunity of attending the first Annual Growth Meeting of the I C C. in Paris. At this meeting all the study groups were represented that were then participating A team was formed with two other members (L. K. L. and H L.), and during the winter of 1954–55 the studies were planned and modelled mainly on the pattern of the London study Much work was expended on elaborating and standardizing the forms, especially the interview forms, and on arranging the forms so that they could be

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child is examined at the clinic at the following ages, 1 month (4 weeks), 3 months (13 weeks), 6 months (26 weeks), 9 months (39 weeks), 1 months, 18 months, years and thereafter once a year. In order that the investigations may be considered to represent actual ages, the following tolerances as regards time are permitted for the age of 4 weeks ± * days, for 3–18 months ± 1 week, for *-3 years ± weeks and subsequently − weeks and + 4 weeks.

At each visit the following examinations and observations are made.

Somatic history is recorded including a general appraisal of health since the last visit and a cl ical examination is performed with a general appraisal of the present condition of health at tus.

Body measurements are taken for 16 different parts of the body area (Fig. 1) including measurements of the kinfolds at four different places.

Roentgenological exam nations of a wrist, ankle and knee are carried out in order to estimat the skeletal development judged by the size and shape of the ossification centers. In addition the calf is also examined to determine the thickness of the soft tissue.

Photographs of the child in different positions are taken. From the f 4 years these re carefully standardized in order to enable sessment of body constitution (Fig. 1).

Psychological interview with special reference to the child functional development and beha iour. They comprise set of detailed question in accordance with standard form nd last about one and half hours. They are focused on different habits and traits as well a on the parents method of handling the child.

Fig. 1. The various body measurements taken.

Up to 3 years these interviews take place only with the mother but when the child is 4 years old the father as well is interviewed (at home). Both parents fill in an ttitude scale (abridged Schaefer Bell) [41]. We also ask them about their attitudes to their own upbringing.

Psychological testing. Starting from the age of 3 months and continuing up to years a psycho-motoric development test for infants (Brunet Lézine [4], a modification of the Gesell test) is used. This test i applied also in the majority of the other centres. At the age of 3 years the intelligence level is assessed by the Terman Mer

TABLE 1 *Study plan*

Investigation	Ant natal period	Neo-natal period	4 weeks	13 weeks	6 weeks	39 week	1 mths.	18 mths.	yrs.	3 yrs	4 yrs.	5 yrs.
Social and home situation							x					
Perinatal history and course												
Physical examination				x				x	x			
Body measurements				x								
X ray					x					x		
Ant natal interview												
Lying in interview												
Psychological interview				x								
Test( )				x								
Ratings				x								

used later for punch-card analysis Meetings arranged by the I C C 1954 Paris 1955 Stockholm 1956 London, 1958 Brussels 1960 Zürich 1962 London [6] and personal contacts have facilitated the co-ordination of these international studies. In 1955 a base-line as a minimum was agreed upon [12] On the other hand each centre has been free to add further investigations

In January 1955 a *Clinic for the Study of Children s Development and Health* was established at Karolinska Sjukhuset in the Children s Hospital and one more member (I S) joined the team Since the number of tasks increased it was found necessary to include another psychologist in the team

Members of the team from the beginning P Karlberg pediatrician head of the team G Klackenberg child psychiatrist I Klackenberg Larsson psychologist H Lichtenstein pediatrician I Svennberg nurse with special training in well baby clinic work

Members associated later on B Olofgörs psychologist (1/3 1958–28/? 1959) K Widstrom psychologist (1/_ 1959–31/3 1960) J Stenson psychologist (from 1/4 1960)

Scope

The general design of the investigation is as follows (Table 1)

Antenatal interview The psychologist visits the expectant mother in her home 1–2 months before the estimated time of delivery in order to establi h contact and introduce the study A short interview is taken mainly concerned with her attitude towards the delivery what sex she wi hes her child to be and her former experience of children

Investigations at the maternity hospital In a *Lying In interview* the psychologist continues the contact with the mother and goes into her experience in connection with delivery and the child s behaviour during the stay in the maternity hospital

Somatic data The pediatrician commences his field work at the maternity hospital He obtains information on the family history including hereditary diseases the mother s antenatal and obstetric hi tory the course of labour and delivery the child s condition immediately after delivery and during the subsequent time in the maternity hospital

Follow up investigations (the main study) After the maternity hospital period the

child is examined at the clinic at the following ages: 1 month (4 weeks), 3 months (13 weeks), 6 months (*6 weeks), 9 months (39 weeks), 1 months, 18 months, * years and thereafter once a year. In order that the investigations may be considered to represent actual ages the following tolerances a regards time are permitted: for the age of 4 weeks ± * days; for 3–18 months ± 1 week; for –3 years ± * weeks and subsequently – weeks and + 4 weeks.

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Body measurements are taken for 16 different parts of the body area (Fig. 1) including measurement of the skinf lds at four different places.

Roentgenological examinations of a wrist nkle and knee are carried out in order to estimate the skeletal development judged by the size and shape of the ossification centers. In addition, the calf is also examined to determine the thickness of the soft tissue.

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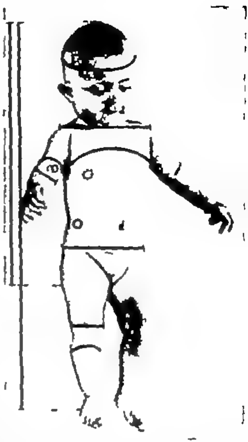

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TABLE 2. *Distribution of groups of gainfully employed population by industry and registration district in Solna Stockholm and Stockholm with inner suburban area* (10[illegible]0)

Industry groups	Solna	Stockholm	Stockholm with inner suburban area
Agriculture f restry and fishing	0 7	0.6	0 5
B ilding	7 5	6.	7.[illegible]
Othe industry handicrafts etc	30.3	28	[illegible]9.5
Transport and communications	1[illegible].5	10	10.3
Distribution	23.3	30 3	[illegible]9 0
General administration and professions	[illegible]2.6	19.3	19 1
Domestic service and unspecified	9	4 0	4 1

rill intelligence test and the child is observed during a free doll play

Rating At each psychological interview with the mother and examination of the child an attempt is made to rate various personality traits on a 5-point scale

Social interview Every year a social interview is arranged covering parents occupation educational level source of revenue dwelling conditions, family com position etc

Each visit to the clinic takes 2½–3 hours The examinations and observations are made by a pediatrician (H L.) a nurse (I S) and 1 or 2 psychologists depending upon the age of the child (I K L. and J S)

During the examinations and the inter views no advice is given to the mother how to care for the child i e the growth study centre is no substitute for a well baby clinic This was clearly stated to the pa rents when the study was introduced. If in need of medical consultation however the mother is encouraged to visit the family doctor or an out patient department The only substantial advantages given to the participants are cover of travel expenses and a print of one of the photographs taken at each visit

Material

On account of the intensity of the study and in accordance with the experi ences of the London team we regarded a sample consisting of 200–250 children as maximum The selection of a sample from the whole of Stockholm including the inner suburban area was not considered possible from a practical point of view especially as our purpose was to make the first contact antenatally A geographically limited and representative recruitment area situated not too far from the Karolinska Sjukhuset was desirable The town of Solna was considered suitable for this purpose

Solna is a part of the conglomerate of communities around Stockholm with about 50 000 inhabitant [47] In spite of the situation on the periphery of a large city Solna can neither be regarded a re presenting the special kind of urban struc

TABLE 3 *Distribution of population by occupational status in Solna Stockholm and Stockholm with inner suburban area* (1950)

Occupational status	Solna	Stockholm	Stockholm with inner suburban area
Self-employed persons	7.5	8.3	8.4
Salaried employees	43 0	47 7	46 8
Wage-earners	49 5	44.0	44.8

ture known as a "dormitory" nor as a particularly industrial district. According to the census taken in Sweden in 19.0 [49] the occupational distribution among the gainfully employed population of Solna agreed well with that of Stockholm and its inner suburban area (Tables and 3) A slight tendency towards a higher propor tion of wage-earners in Solna may how ever be noticed The d stribution of votes among the political parties at the election in 195_ and 1954 [5, 8] in Solna and Stockholm are in close agreement (Table 4)

The topography of Solna is also favour able The built-up areas show great variation. The town is in a progressive phase of its history with the development of new residential areas and modernization of the old (for further description see Paper II of this series [23]).

Finally the fact that Karolinska Sjuk

TABLE 4 *Th distribution of vote mong the political parties at the elections* (a) *in 1952 and 1954 and* (b) *i 1956 and 1958*

(Results in per cent)

Pol ical parties	Solna Communal election	Solna Election to the 2nd Chamber of the Riksdag	Solna Combined	Stockholm Communal election	Stockholm Election (the 2nd Chamber of the Riksdag	Stockholm Combined
( )	*1952*	*1954*	*1952 1954*	*1952*	*1954*	*1952 1954*
Tory	13.3	15 7	18 8	18 2	20 4	19.2
Liberal	31 4	29 8	3_.1	34.3	31 1	33 7
Social Democrat	43.3	43 8	43.6	39.0	40.7	39 7
Communist	8 8	9 0	8.8	6.5	7 9	7 4
Other	0 2	—	0 1			
(b)	*1956*	*1958*	*1956 1958*	*1956*	*1958*	*1956 + 1958*
Tory	[illegible]	19	23 6	20 9	23 9	24.8
Liberal	19 2	31.9	25 2	35 6	19 4	27 6
Social Democrat	43 6	39 9	41.3	36 6	42.6	40 0
Communist	7.6	9 7	8 7	6.9	6.2	6 6
Other	2 3	0 2	1.3	0.1	0	1.0

TABLE 2. *Distribution of groups of gainfully employed population by industry and registration district in Solna, Stockholm and Stockholm with inner suburban area* (1960)

Industry groups	Solna	Stockholm	Stockholm with inner suburban area
Agriculture, forestry and fishing	0.7	0.6	0.8
Building	7.8	6.7	7.[illegible]
Other industry, handicrafts etc.	30.3	[illegible]3.7	[illegible]9.5
Transport and communications	1[illegible].8	10	10.3
Distribution	23.3	30.3	[illegible]9.0
General administration and profession	22.5	10.3	19.1
Domestic service and unspecified	9	4.0	4.1

rill intelligence test and the child is observed during a free doll play.

Rating. At each psychological interview with the mother and examination of the child an attempt is made to rate various personality traits on a 5-point scale.

Social interview. Every year a social interview is arranged covering parents' occupation, educational level, source of revenue, dwelling conditions, family composition etc.

Each visit to the clinic takes 2½–3 hours. The examinations and observations are made by a pediatrician (H. L.), a nurse (I. S.) and 1 or 2 psychologists depending upon the age of the child (I. K. L. and J. S.).

During the examinations and the interviews no advice is given to the mother how to care for the child, i.e. the growth study centre is no substitute for a well baby clinic. This was clearly stated to the parents when the study was introduced. If in need of medical consultation, however, the mother is encouraged to visit the family doctor or an out patient department. The only substantial advantages given to the participants are cover of travel expenses and a print of one of the photographs taken at each visit.

Material

On account of the intensity of the study and in accordance with the experiences of the London team, we regarded a sample consisting of 200–250 children as maximum. The selection of a sample from the whole of Stockholm including the inner suburban area was not considered possible from a practical point of view, especially as our purpose was to make the first contact antenatally. A geographically limited and representative recruitment area situated not too far from the Karolinska Sjukhuset was desirable. The town of Solna was considered suitable for this purpose.

Solna is a part of the conglomerate of communities around Stockholm with about 50 000 inhabitants (4[illegible]). In spite of the situation on the periphery of a large city, Solna can neither be regarded as representing the special kind of urban struc

TABLE 5 Number of children investigated at different ages

	1 mth.	3 mths.	6 mths.	9 mths.	12 mths.	18 mths.	2 yrs	3 yrs.	Total
Complete investigations on the correct date	199	199	196	194	203	188	196	202	1567
Complete investigations on incorrect date	7	3	2	4	2	7	3	2	30
Somatic investigation only	3	2	0	0	0	0	0	0	5
Psychological investigation only	0	0	1	1	3	0	2	2	9
No investigation	13	14	13	9	4	15	6	3	77
Total	212	212	12	12	212	10	209	209	

time a random selection of prospective mothers from the clientele of a gynecologist with a private practice in Solna had also been agreed upon. It was found, however, that the 183 children comprising the ANC group taken together with the 29 children of the pilot study afforded a good agreement with the socio-economic class distribution of families in Stockholm (see page 19). A selection from the clientele of a gynecologist would not have been unexceptionable either from a statistical point of view. Therefore the preliminary plan was not carried out.

A contributory factor in stopping of the recruitment at this point was that it continuation would have meant an increase ... which was not considered feasible having regard to the financial ... available at that time.

It was then decided that the material for study should consist of the 183 children from the Solna Antenatal Clinic and the 29 children from the pilot group, making a total of 212 children.

Course of the Study up to the Time when all Children had Reached 3 Years of Age

The recruitment of the 21 children was completed after a period of 3 years; the annual distribution is shown in Fig. ... It also gives the age distribution on 31 March 1961: the oldest children were then 8 years old and the youngest 3.

Losses. On 1 April 1961 there were still 209 children taking part in the investigation. Of 3 children who had so far dropped out, ... had been taken to west Sweden at the age of one year and 1 to the United States at the age of 18 months.

In general the interest shown by the families participating in the investigation has been most satisfactory and in those cases where difficulties have arisen owing to, for instance, the participant's work proving an obstacle or to hesitation in general, the study group has done all in its power to facilitate continued participation. It has been possible for the Clinic to keep in touch also with representatives of more extreme social, economic and

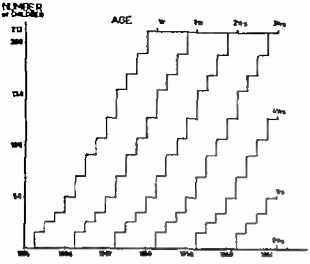

Fig A diagram showing the intensity of recruitment during the time period of 1 April 1955 to 31 March 1958 as well a the age distribution of the material at any quarter of the years up to 31 March 1961 when all children had reached the age of 3 years.

huset is situated in the town of Solna was an advantage of practical significance

Recruitment started in the beginning of 1955 At first a test group of 12 children aged 1–18 months was formed in order to test methods and procedures Of these 7 are still being studied but the data on them will not be included in the analysis of the final material.

Up to December 1955 a pilot group *comprising* 29 *children* was *enrolled* In these cases the first contact was made either antenatally or neonatally They were mainly recruited from the Obstetrical Department of Karolinska Sjukhuset (21 cases) The remainder consisted of expectant mothers with whom contact had been established through the personnel at child welfare centres

From December 1955 subjects were recruited exclusively from the Solna Antenatal Clinic *Every fourth expectant* mother according to her registration number was *asked* whether she was willing to allow her prospective child to participate in the investigation Seventeen of these mothers—in the beginning registered at the Antenatal Clinic—had already moved from Solna before we began to contact mothers the offer was then made to the next 4th expectant mother selected at *random The same procedure* was adopted if mothers were unable to participate for any other reason such as lack of interest on their own part or of their husbands or fiancés (7 persons) In a longitudinal study which on account of the repeated time-consuming and comprehensive investigations may prove burdensome to the family it is inevitable that already at the onset some of the randomly selected participants should withdraw The number of these cases was small however only 3 per cent of all those who were invited to take part in the investigation

Of the 198 mothers who stated that they were willing to participate 0 fell out on account of abortion and 4 on account of the child s death in connection with delivery Furthermore, 5 were excluded because of the premature birth of the child whose weight at birth was under *2000 grams in view of the fact that* such children represent an extreme group with a special course of development [67]

In this way up to April 1958 183 children were recruited from the Solna Antenatal Clinic for the study (= ANC group) A preliminary estimate of the socio-economic *composition of this group showed* a certain shift in the direction of the lower *socio-economic groups as compared* with Stockholm (see discussion on the representativeness *of the material below*) This was expected and as an attempt to counterbalance the selection from an antenatal

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	1 mth.	3 mths.	6 mths.	9 mths.	12 mths.	18 mths.	2 yrs.	3 yrs.	Total
Complete investigations on the correct dat	189	193	196	198	200	198	198	202	1567
Complete investigations on incorrect dat	7	3	3	4	2	7	3	2	30
Somatic investigation only	3	3	0	0	0	0	0	0	6
Psychological investigation only	0	0	1	1	3	0	3	3	9
No investigation	13	14	13	9	4	11	6	3	77
Total	212	212	212	212	212	210	209	209	

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Course of the Study up to the Time when all Children had Reached 3 Years of Age

The recruitment of the 212 children was completed after a period of 3 years; the annual distribution is shown in Fig 2. It also gives the age distribution on 31 March 1961 the oldest children were then 6 years old and the youngest 3

Losses On 1 April 1961 there were still 209 children taking part in the investigation. Of 3 children who had so far dropped out, 2 had been taken to west Sweden at the age of one year and 1 to the United States at the age of 18 months.

In general the interest shown by the families' participation in the investigation has been most satisfactory and in those cases where difficulties have arisen owing to for instance, the participant's work proving an obstacle or to hesitation in general the study group has done all in its power to facilitate continued participation. It has been possible for the Clinic to keep in touch also with representatives of more extreme social, economic and

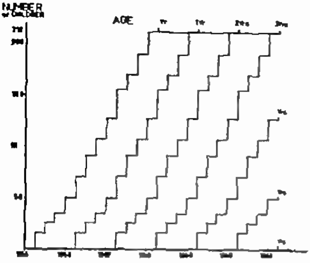

Fig — A diagram showing the intensity of recruitment during the time period of 1 April 1955 to 31 March 1958 as well as the age distribution of the material at any quarter of the years up to 31 March 1961 when all children had reached the age of 3 years.

huset is situated in the town of Solna was an advantage of practical significance

Recruitment started in the beginning of 1955 At first a test group of 12 children aged 1–18 months was formed in order to test methods and procedures Of these 7 are still being studied, but the data on them will not be included in the analysis of the final material

Up to December 1955 a pilot group comprising 29 children was enrolled In these cases the first contact was made either antenatally or neonatally They were mainly recruited from the Obstetrical Department of Karolinska Sjukhuset (21 cases) The remainder consisted of expectant mothers with whom contact had been established through the personnel at child welfare centres

From December 1955 subjects were recruited exclusively from the Solna Antenatal Clinic Every fourth expectant mother according to her registration number was asked whether she was willing to allow her prospective child to participate in the investigation Seventeen of these mothers—in the beginning registered at the Antenatal Clinic—had already moved from Solna before we began to contact mothers the offer was then made to the next 4th expectant mother selected at random The same procedure was adopted if mothers were unable to participate for any other reason such as lack of interest on their own part or of their husbands or fiancés (7 person) In a longitudinal study which on account of the repeated time-consuming and comprehensive investigations may prove burden some to the family it is inevitable that already at the onset some of the randomly selected participants should withdraw The number of these cases was small however only 3 per cent of all those who were invited to take part in the investigation

Of the 198 mothers who stated that they were willing to participate 6 fell out on account of abortion and 4 on account of the child's death in connection with delivery Furthermore 5 were excluded because of the premature birth of the child whose weight at birth was under 2000 grams in view of the fact that such children represent an extreme group with a special course of development (67)

In this way up to April 1958 183 children were recruited from the Solna Antenatal Clinic for the study (= ANC group) A preliminary estimate of the socio-economic composition of this group showed a certain shift in the direction of the lower socio-economic groups a compared with Stockholm (see discussion on the representativeness of the material below) This was expected and as an attempt to counter balance the selection from an antenatal

TABLE 5 *Number of children investigated at different ages*

	1 mth.	3 mths.	6 mths.	9 mths.	12 mths.	18 mths.	2 yrs.	3 yrs.	Total
Complete investigations on the correct date	190	193	196	198	203	188	198	*03	1567
Complete investigations on incorrect dat	7	3	3	4	2	7	2	2	30
Somatic investigation only	3	2	0	0	0	0	0	0	5
Psychological investigation only	0	0	1	1	3	0		2	9
No investigation	13	14	[illegible]	9	4	15	6	3	77
Total	212	212	212	212	212	210	209	209	

clinic a random selection of prospective mothers from the clientele of a gynecologist with a private practice in Solna had also been agreed upon. It was found, how ever that the 183 children comprising the ANC group taken together with the 29 children of the pilot study afforded a good agreement with the socio-economic class distribution of families in Stockholm (see page 19) A selection from the lientele of a gynecologist would not have been unexceptionable either from a statistical point of view Therefore the preliminary plan not carried out

A contributory f ctor in stopping of the recruitment t this point was that ts continuation would have meant an increase in staff which wa not considered feasible having regard to th financial id available t that t me

It wa then decided that the material for study should consist of the 183 children from the Solna Antenatal Clinic and the 29 children from the pilot group, making a total of 1 children

Course f the Study up to the Time when all Children had Reached 3 Years of Age

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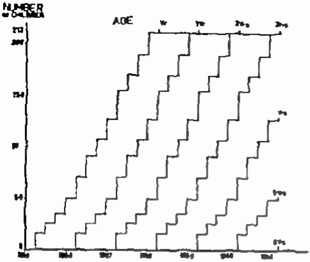

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TABLE 6. *The socio-economic classification of the pilot group the ANC group the total material and families with school-children in Stockholm* (see text)

Social group	Pilot group (= 29) number	%	AKO group (n = 183) number	%	Total sample (= 212) number	%	Stockholm families with schoolchildren (= 238), %
I	(13)	45	(21)	12	(36)	17	16
II	(11)	38	(68)	38	(79)	37	38
III	(5)	16	(93)	51	(98)	46	46

ing distribution was obtained when selecting at random families with boys of school age: Group I 16 %, Group II 38 %, Group III 46 %. When these figures are used for comparison (Table 6) the ANC sample is found to display a slight shift in the direction of a lower social grouping. Such a result could be expected. First, it is probable that expectant mothers who go to antenatal clinics do not entirely represent the society as a whole. Secondly we do *not know exactly* how *similar* the data of social groupings in Stockholm and in Solna are but, as previously shown the differences between the two towns with regard to the distribution of occupations and of votes t the political elections, are inconsiderable (Tables 2 3 and 4) Another possible cause is that the inevitable loss in the line of *every 4th* expectant mother from the Antenatal Clinic may give rise t an undue distribution In order to judge the influence of the last mentioned cause the mothers in question have been *classified* from the socio-economic standpoint A combination of the ANC group and the group *comprising* the loss of cases did not show any significant shift (Group I 10 ., Group II 41 ., and *Group* III 48). Probably the selection from clientele of an antenatal clinic had the greatest influence

The pilot group which represents the minor part (14 %) of the material studied, was recruited mainly from the Obstetrical Department of Karolinska Sjukhuset That these cases were chosen from a hospital population does not in itself imply a selection, since 98.5 per cent of all children in Stockholm, as in other parts of Sweden are born in a hospital [38, 39] On the other hand, the character of the hospital as a university hospital may be of significance This group included also expectant mothers with whom we came into contact through the personnel of child care centres. This probably means a selection of mothers who are *willing* to cooperate. As regards classification into social classes the pilot group showed a *marked shift in the* direction of higher social classes (Table 6)

A combination of the two groups (Table 6) showed very good agreement with the corresponding socio-economic class *distribution* in Stockholm families with boys t school, selected at random [19] Consequently we considered that the two groups together should constitute a material which, from socio-economic point of view should be better representative of *children in Stockholm* and the suburban rea than the ANC group lone

On the basis of the official statistics available in Sweden the representative-

psychological conditions for whom participation might have been expected to be a burden.

Investigations conducted Over 1 800 investigations were carried out Table 5 shows the number of investigations made for the respective ages until the children were 5 years old There were 1,5?0 complete examinations carried out on the correct date The table gives also the number of examinations made on the incorrect date as well as those which were not made at the different ages because of unavoidable circumstances, for example the child s illness or the family being away on holiday

Representativeness of the Material

In a study of growth and development it is essential to know from which population the sample is taken and to what extent it is representative and whether it includes any special features

Selection of material and socio-economic evaluation

The purpose of the study was to investigate children who grow up in a Swedish urban community The town of Solna was chosen as being the most suitable in the region of Stockholm

A perfect random sampling for an investigation of this kind would require among other things a register of all women in Solna who were pregnant during a given time period This was not possible to obtain

A random selection of expectant mothers registered at the only Antenatal Clinic located in Solna was considered the best course within the practical possibilities although this procedure would imply certain limitations. The clientele of a maternity welfare centre cannot be regarded entirely representative of an average population of expectant mothers One can assume even though no direct investigations are available that the most well-to-do and some with a previous bad obstetrical history go to private gynecologists or to an outpatient department of a hospital Moreover other selective factors are conceivable such as the loss of selected expectant mothers who move away before the birth of the child and of mothers who have miscarriages stillbirth or a child who dies neonatally as well as the loss of some women who refuse to take part in the investigations These are all unavoidable circumstances in any investigation of this kind

Consequently the representativeness of the *ABC group* (see page 16) had to be tested In the first place the group was evaluated from a socio-economic point of view A three graded social grouping system widely used in Sweden was employed This pays special attention to paternal occupation (group I represents the highest group [9]) The distribution obtained is shown in Table 6 No comparative classification was available for the town of Solna however and therefore the corresponding figures for Stockholm had to be used

The distribution by social groups in connection with the elections in Stockholm [5? 53] is less suitable for the comparison since it includes all persons eligible to vote young and old married and single There are reasons for assuming that the distribution in such a population is somewhat different from that among families with children More adequate for our evaluation are the findings of Jonsson Kalvesten s investigation of Stockholm boys which they carried out in 19?4–19?8 [10]. The follow

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A combination of the two groups (Table 6) showed very good agreement with the corresponding socio-economic class distribution in Stockholm families with boys at school, selected at random [10]. Consequently we considered that the two groups together should constitute a material which from a socio-economic point of view should be better representative of children in Stockholm and the suburban area than the ANC group alone.

On the basis of the official statistics available in Sweden the representative-

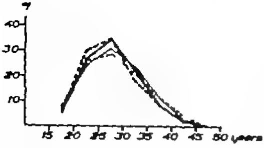


Fig 3

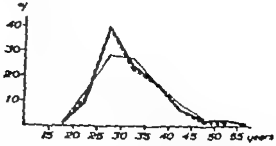


Fig 4

Fig 3 Mothers ages at children s birth —— in ANC group (n = 183) —— in total growth study (n = 12) —— in population of Stockholm 1956–57 —— in population of Sweden 1956–57

Fig 4 Fathers ages at children s birth —— in ANC group (married fathers n = 155) —— in total growth study (married fathers n = 166) —— in population of Sweden (married) 1956–57

ness of the sample can be further evaluated in the first place in respect of parent s age civil status of the mother at birth of the child and order of sequence among the siblings This information is obtained from the investigation of the social and family background (see scope of study) Both the ANC group and the total material have been evaluated in these respects The comparative figures are taken when not stated for the years 1956–1957 during which period most of our children were born

Mother s age (when the child was born)

The mothers age distribution is shown in Fig 3 For purposes of comparison the distributions of mothers in Stockholm [50] and in the whole of Sweden [46] are also given Since the children were recruited irrespective of their order of sequence the diagram represents a mixture of primiparae and multiparae The curves give a cross-section of the mothers ages at child birth There is good agreement especially with the population of Stockholm with a tendency towards younger ages which is less pronounced in the total material than in the ANC group

Father s age (when the child was born)

The fathers age distribution is given in Fig 4 Comparative adequate official data for Solna Stockholm and Swedish urban populations are lacking The comparison that was possible to make covers fathers of children born in wedlock in the whole population of Sweden [20 33] The corresponding ages of the married fathers included in the study are shown in the dashed distribution curve in Fig 4 A tendency towards younger fathers is evident but no difference between the ANC group and the total material

Civil status of the mother (when the child was born)

Out of the 212 children included in the study 89 2 per cent were born in wedlock and consequently 10 8 per cent of the mothers were unmarried. For the ANC group the corresponding figure was 1 [illegible] per cent The number of children born (live births) out of wedlock in Sweden has been rather constant in recent years it is somewhat higher in the town than in the rural districts The percentual mean value for the years 1955–1958 was 10 1 for Sweden as a whole 10 4 for the towns and

0.8 for the rural districts [*8 32 36 37] The corresponding figure for the city of Stockholm is 11.6 [51 54]. Thus the percentage of children who were born out of wedlock corresponds to the mean value for Swedish towns and for Stockholm during the period of recruitment.

It was possible also to estimate the time of delivery in relation to the time when the marriage was contracted. There is good agreement with the official statistics for Stockholm [53] as illustrated in Table 7

Table 7 *Duration of marriage at birth of child*

Duration of marriage at birth of child	ANC group (n = 161) %	Total material (n = 190) %	Stockholm (1956–57) %
< 9 months	26	22	21
9 months–2 years	16	17	16
2 years–5 years	22	24	29
> 5 years	36	37	35

The child's successional number

Table 8 shows the distribution of the children according to their successional numbers at birth. A combination of the ANC group with the pilot group does not appreciably change the figures, nor does a combination of the ANC group with the loss during recruitment To base a comparison on the official Swedish statistics is possible only with regard to children born in wedlock where the marriages were contracted in 1950 or later

Of the Swedish children born in wedlock in 1956 and 1957 2.6 per cent are the issue of marriages contracted in 1950 or later [31 35]. For our corresponding material the figure is 72 per cent (152 children). Conditions in the comparable part of the sample (born in wedlock, marriages contracted in 1950 or later) and the corresponding condition in Solna and other urban population in Sweden are shown in Table 8 Information on the town of Solna is taken from the primary material available at the Central Bureau of Statistics. There is good agreement between our material and comparable figures for the town of Solna

It was possible to judge another aspect of the firstborns who were the issue of marriages contracted in 1950 or later Of these 78 children, 44 per cent were born less than 9 months after the marriage ceremony According to official statistics the corresponding percentage for Swedish firstborns in 1956 and 1957 was 45.5 per cent and 44 per cent respectively [30 34]. Here, the material covered by the study corresponds to conditions which are

Table 8 *Distribution of the children according to their order of sequence at birth*
(The twins in the three pairs have been given the same successional number)

	ANC group (n = 163) %	Total group (n = 212) %	ANC group + loss during recruitment (n = 222) %
Order of sequence			
1st	42	40	42
2nd	40	42	40
3rd or later	19	18	18

In marriages established 1950 or later	Total group (n = 152) %	Urban population in Sweden (1956 and 1957) %	Solna town (1956 and 1957) (n = 1212) %
Order of sequence			
1st	61	56	57
2nd	35	35	37
3rd or later	4	10	6

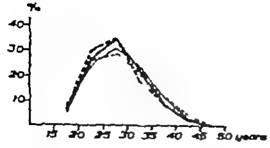
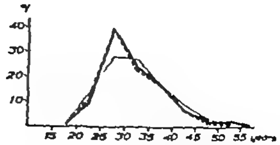


Fig. 3



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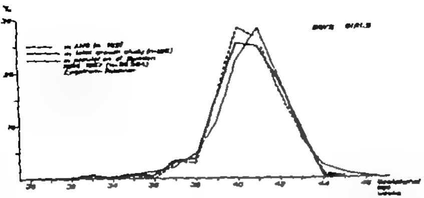


Fig 5. Children's gestational age at birth in the AXO group, in the total material, and in the population of Sweden 1956–57 (Engstrom-Falconer).

are, on the other hand, of greater importance in evaluating the representativeness of the material. The distribution of these parameters is given in Tables 10 and 11. During the period 1 July 1956–30 June 1957 Engström and Falconer made a survey supported by the Government, of weight and length at birth in relation to gestational age for all live-born newborns in Sweden [11]. An analysis of their material was made after the exclusion of twins and triplets, newborns of diabetic or toxaemic mothers, and all children with malformations. After excluding similar

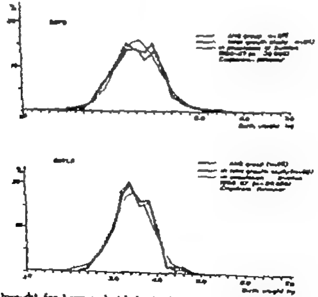


Fig 6. The birthweight for boys and girls in the AXO group, in the total material, and in the population of Sweden 1956–57 (Engström Falconer).

TABLE 9 *Incidences of some important perinatal factors in the total material*

	Number	% (n - 1)
Toxaemia	9	4.2
Diabetes	0	0
Medical induction of labour	2	0 9
Breach	4	1 0
Forceps (low)	4	1 9
Caesarean section		0 9
Resuscitation	3	1 4
Duplex	3	1 4

known. The comparison however has a restricted value since as regards first-borns it was not possible to give figures for an urban as opposed to a rural population.

Perinatal factors

Perinatal factors are of importance also for the evaluation of the general properties of the material Table 9 shows the incidence of some significant perinatal factors No higher incidence was found to occur in the pilot group It is hazardous

TABLE 10 *Distribution of gestational age.*

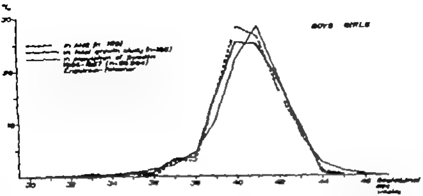
Gestational age in weeks	ANC group (n - 183) n	Total material (n - 212) n
33	—	1
34	—	—
35	1	1
36	—	1
37	6	7
38	7	11
39	29	33
40	40	51
41	44	48
4	[illegible]	36
43	15	10
44	1	1
Undetermined	3	3

to draw conclusions concerning the frequencies of factors which occur so seldom in our material. However if an evaluation is made from the annual reports of maternity hospitals in the Stockholm region [69] it would seem that perinatal complications are not overrepresented but possibly slightly underrepresented in our material This may be due to the exclusion of still births and neonatal death and to the small number of prematures. Moreover it is probable that cases with an earlier bad obstetrical history often receive antenatal care at a hospital and not to such a great extent at antenatal clinics The frequency of irreversible damage to children injured by perinatal factors is, however so low that a study designed on the lines of the present investigation can not be expected to afford significant information on these conditions.

Gestational age and weight at birth

TABLE 11 *Distribution of birth weight for boys and girls*

Birth weight in kg	Boys: ANC group (n - 103) n	Boys: Total material (n - 122) n	Girl: ANC group (n - 80) n	Girl: Total material (90) n
..00-2 19	1	1	—	—
..20-2.39	—	—	—	—
..40-2.59	2	3	1	1
2.60-2.79	3	6	4	4
..80-2.99	9	9	6	7
3.00-3 19	10	1	10	11
3.20-3.39	13	[illegible]	17	19
3.40-3.59	17	19	14	15
3.60-3 79	12	14	10	14
3.80 3 99	11	16	15	16
4 00-4 19	16	19		
4.20-4.39	4	4	—	—
4 40-4.59	2	3	1	2
4 60-4 79	1	1		
4.80-4 99	1	1		
5 00-5.19	—	—		
5.20-5 39	1	1		



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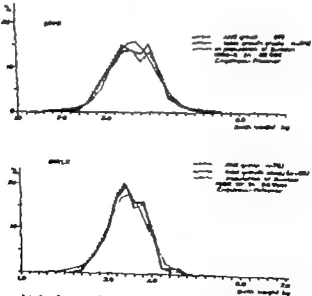

Fig 4. The birthweight for boys and girls in the ANU group, in the total material, and in the population of Sweden 1956–57 (Engström-Falconer).

cases ($n = 13$) the gestational age and weight at birth in the ANC group and in the total material were compared with the results of this survey (Figs 5 and 6). There was good agreement with a slight tendency towards lower values in our material. The evident broader range of birth weight for the boys in relation to the girls in the large Engström–Falconer material is closely followed by our material which supports its representativity.

Sex distribution

Another property of the studied material with importance for its representativity is the sex distribution. The ANC group consists of 56.3 per cent boys and 43.7 per cent girls and the total group of 57.5 per cent boys and 42.5 per cent girls. In the town of Solna 52.1 per cent boys and 47.9 per cent girls were born during the years 1956 and 1957 [43] which means an increased proportion of boys in relation to the whole country (51.6 per cent boys) [47]. The high frequency of boys in our material is nevertheless conspicuous. However a t test does not show any significant percentage difference ($P > 0.05$).

Conclusion

On account of the preliminary socio-economic evaluation recruiting was concluded with the ANC group. The pilot group and the ANC group taken together showed in this respect a better agreement with conditions in Stockholm than the ANC group alone. There are reasons to believe that this holds good for both Solna and Stockholm with its inner suburban area. Further analyses have shown that in other respects such a combination does not seem to affect the representativeness of the material in a negative direction.

The practical difficulties associated with adequate sampling have unfortunately been great. If the children had been selected after birth a sampling technique which was statistically more strict could have been applied. Although the data obtained during the antenatal interview do not form an essential part of the total data collected in our opinion the antenatal contact with each expectant mother and also with many of the fathers was of great value for cooperative participation in the study.

However the group of children obtained by means of the techniques used showed good agreement in most respects when comparisons were possible with conditions known to prevail in the large urban area from which the material originated. Apart from the composition of the social group this applies also to the mothers' age, the percentage of children born out of wedlock, the time when the children were born in relation to the time when marriage was contracted, the children's successional number, the stated period of pregnancy in weeks and the children's weight at birth.

The frequency of boys in relation to that of girls does not differ by more than can be attributed to chance in the differences that exist in statistically unexceptionable samples recruited from the same population group. The difference obtained cannot be due to any special selection because the main group of the sample was chosen before the birth of the children. Nor can this sex distribution give rise to any skewness in the results since in the analyses of the combined data where sex may be regarded as of importance the sampl[illegible]

divided into boys and girls. Only the values obtained for the girls are based on a somewhat smaller number than those for the boys.

A further point to be observed is the composition of the pilot group in which social group I is over represented. On account of the recruiting method applied the pilot group probably contains a higher percentage of mothers who are more willing to cooperate. This should be borne in mind with reference to analyses of data from social group I in the total material.

We have considered it important to carry out these analyses, since the more similarities that can be established, the stronger are the reasons to assume that the study will furnish data that have a wider application than merely to the group investigated. Hence when we subsequently present frequencies and tendencies regarding somatic and psychic data we may do so with a degree of confidence based on the above-mentioned considerations.

Summary

The first Swedish prospective longitudinal investigation into the development of children in a Swedish urban community is presented. Its aims, design and recruiting procedure are described, and the representativeness of the material obtained is discussed. The investigation forms a link in an internationally coordinated study.

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cases ($n = 13$) the gestational age and weight at birth in the ANC group and in the total material were compared with the results of this survey (Figs. 5 and 6). There was good agreement with a slight tendency towards lower values in our material. The evident broader range of birth weight for the boys in relation to the girls in the large Engström–Falconer material is closely followed by our material which supports its representativity.

Sex distribution

Another property of the studied material with importance for its representativity is the sex distribution. The ANC group consists of 56.3 per cent boys and 43.7 per cent girls and the total group of 57.5 per cent boys and 42.5 per cent girls. In the town of Solna 52.1 per cent boys and 47.9 per cent girls were born during the years 1956 and 1957 [43], which means an increased proportion of boys in relation to the whole country (51.6 per cent boys) [47]. The high frequency of boys in our material is nevertheless conspicuous. However a t test does not show any significant percentage difference ($P > 0.05$).

Conclusion

On account of the preliminary socio-economic evaluation recruiting was concluded with the ANC group. The pilot group and the ANC group taken together showed in this respect a better agreement with conditions in Stockholm than the ANC group alone. There are reasons to believe that this hold good for both Solna and Stockholm with its inner suburban area. Further analyses have shown that in other respects such a combination does not seem to affect the representativeness of the material in a negative direction.

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The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study

II The Social Background and its Changes During the Children's First Three Years of Life

by GUNNAR KLACKENBERG PETTER KARLBERG INGRID KLACKENBERG-LARSSON HENRIK LICHTENSTEIN JAN STENSSON and INGA SVENNBERG

It is a generally accepted fact that a child's growth and development are influenced by the social environment In the present longitudinal study the social data including the family background form an essential part of the investigations (see the scope of the study in Paper I of this series [7])

The detailed analysis of the social environment of the 212 studied children has two main aims 1) evaluation of the representativeness of the studied group of children and 2) evaluation of the relation between the social background with its changes and the child's development The purpose of this report is to provide the base material by describing and defining the social background The representativity of the studied children has been discussed in Paper I [7]

The social data will be divided into the following main groups type of district from which the families were recruited housing condition in respect of occupant density and comfort parents education their occupation source and size of income and composition of the family including age and civil status of the parents Although several of these items will be used separately for later correlative analyses of collected data it is obvious that some kind of condensation of the social data into a social grouping system would be very useful As this Swedish study constitutes a link in internationally coordinated studies (see Paper I [7]) such a system might also form a basis for international comparison At the beginning of these international studies Graffar the leader of the Brussel study group elaborated a social grouping system for this purpose [3] It is based on 5-point scales for five different criteria which include occupation level of education main source of family income quality of dwelling and type of inhabitated district This Graffar system has been applied in the present study and its application will be discussed It will also be compared with the customary Swedish classification into three social groups based mainly on the father's occupation

The picture of the social condition and their changes during the first 3 years of life of the children investigated also have a wider application than to this particular group of children since the sample has been shown to be representative in several respects of children living in Stockholm with its inner suburban area (see Paper I [ ])

Material

The study covers the social background of 212 children with their families. The recruitment took place during the period April 1955–March 1958, and the methods of recruitment have been described in Paper I [7]. The main recruitment area was Solna, town close to Stockholm. Only 3 of the original 212 children participating in the study have been lost sight of during their first three years [7].

Method

The data of social conditions were obtained mainly from interviews with the mothers when the children were 1, 2 and 3 years old. The data recorded are those given in Appendix in Modern Problems in Pediatrics V [4]. Some of these data, for instance the housing conditions, have also reference to the time of the child's birth. Supplementary information has been collected through home visits. In order to ensure a uniform standard of judgement, replies have been scrutinized and discussed within the team.

Owing to the loss of 3 of the 212 children, and since all data were not always obtainable, the calculations of the distribution of different items had to be based on slightly varying numbers. This is indicated, however, in the heading of each table.

The Area in Which the Children Lived

Solna forms a part of the conglomerate of communities which constitute Greater Stockholm. Solna includes within its area a number of newly erected hypermodern blocks alternating with older houses in relatively good repair, and of old residential areas which, without being actually called slums, represent the most unmodern dwellings in the Stockholm of today, without central heating or other amenities. The older houses for one or more families are usually built of wood and have sometimes garden plots. Within the urban district there are also factories, but these do not dominate the scene and consequently the area cannot be characterized as particularly industrial. Though many of the Solna families earn their living in Stockholm, Solna cannot be regarded as the special kind of urban structure known as a "dormitory" (often situated on the periphery of large cities). In Solna there are shops of different sizes, offices, artisans and small-scale factories. The town is in a rapidly progressive phase of its history with the development of new residential areas and modernization of the old ones.

During the children's first 3 years of life, however, a number of their families moved from their original homes. At the age of 3 years the situation of the 209 families remaining in the study was the following:

- 163 families living in Solna.
- 33 families living within the inner suburban area of Stockholm.
- 3 families living within the outer suburban area of Stockholm.
- 10 families living outside Stockholm and suburbs.

Of the ten families who have moved from the Stockholm area, three still live in towns. All ten children have been retained in the study.

In the Graffar system of social grouping one of the five criteria is the type of district in which the families live. This classification is not applicable to Solna, since for the most part there are no distinct demarcations between the different types of district. The Graffar classification is based on areas with bigger differences between districts. Graffar realized [4] that this criteria may be very difficult or even

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TABLE Housing conveniences

	Age of children							
	At birth (n = 212)		1 year (n = 211)		3 years (n = 201)		5 years (n = 206)	
	n	%	n	%	n	%	n	%
Central heating	163	79	168	80	167	83	172	83
Tile stoves and/or iron stoves (oil coke electricity)	44	21	43	20	34	17	34	17
Hot water and bathroom	142	67	153	73	156	77	162	79
Hot water, no bath	14	7	8	4	5	3	3	1
Cold water supply	49	24	44	21	30	15	37	18
No water supply	6	3	5	2	3	2	3	1
Own W.C.	180	85	185	89	180	90	187	91
Shared W.C. or earth closet	8	4	8	4	3	2	3	2
Earth closet outside of the house	24	11	16	8	13	6	13	6

The figures show that dwelling space is very restricted. When the mothers came home from the maternity hospital nearly one third of the families had to live in dwellings with or more persons per room (Table 1).

When the children were 1 year old 22 of the families still lived in these restricted conditions. In these calculations the word room is understood to mean also a kitchen provided it is large enough to sit eat or sleep in. (Practically 100 per cent of the households have their own kitchens: at birth of the children 96 at 1 and 3 years of age 98 %, at 5 years of age 99.5 %.)

The high incidence of restricted dwelling space is not a unique phenomenon for our families. The same is found in Swedish official housing investigation [8]. In a recent socio-psychological study by Jonsson and Kalvesten [6] of a random sample of families with boys of school-age in Stockholm 22 were living in restricted dwelling space. The used as criterion of overcrowding more than persons per room. This is the generally used norm in Sweden [9]. In these calculations however the kitchen is not included as a separate room. If this norm for overcrowding is applied to our study at the birth of the children and on their first and third birthdays then the percentage of overcrowding is more striking: 51, 43 and 28 per cent respectively. When comparing these results it should be borne in mind that Jonsson-Kalvesten's investigations deals with children of school-age and that in our families there is a tendency to less restricted dwelling space with increasing age of the children.

The overcrowding of the families with small children is indeed conspicuous.

Another indication of the living-space standard of family is the extent to which the child has a room of its own or shared with its siblings. The distribution is shown in Table 1. A shift towards better living space with increasing age of the child up to 3 years is again obvious.

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We have taken account of the following conveniences: heating system, water supply, bath and W.C. (Table ?). Fairly modern flat, i.e. with central heating, hot water, bathroom and W.C., are the domi

TABLE 1 *Types of dwelling and dwelling space*

	At birth (– 1)		Age of children 1 year (– 11)		years (– [illegible]01)		3 years (– [illegible]06)	
	n		n		n		n	
Rented flat	190	*91*	198	*91*	184	*[illegible]*	18[illegible]	*91*
Two-family house	7	*3*	7	*3*	7	*4*	3	*1*
One family house	6	*3*	6	*3*	10	*5*	16	*[illegible]*
1 room	3	*1*	1	*0 4*	0	*0*	0	*0*
[illegible] rooms	83	*39*	61	*30*	48	*[illegible]*	3	*1[illegible]*
3 rooms	[illegible]	*36*	83	*39*	[illegible]	*39*	[illegible]	*33*
4 rooms	3	*15*	50	*[illegible]*	57	*[illegible]*	5	*[illegible]*
5 rooms	13	*6*	10	*5*	11	*5*	[illegible]3	*11*
> 5 rooms	5		3	*1*	7	*3*	11	*5*
Up to ½ room/person	64	*30*	46		36	*18*	4	*1*
Up to ¾ room/person	83	*39*	86	*41*	[illegible]0	*39*	78	*3[illegible]*
Up to 1 room/person	5	*3*	60	*[illegible]*	66	*33*	[illegible]7	*3*
> 1 room/person	13	*6*	19	*9*	[illegible]0	*10*	[illegible]7	*13*
Separate room for children	6	*1*	35	*17*	39	*19*	[illegible]0	*31*
Separate room for children only at night	14	*7*	14		[illegible]3	*11*	14	*7*
No separate room for children	17[illegible]	*81*	16[illegible]	*[illegible]*	139	*69*	1[illegible]	*59*

By room is meant also a kitchen provided that it is large enough to sit, eat or sleep in.

impossible to apply in some places and proposed that in such cases only the other four criteria should be used. This is what will be done in the present study.

Housing Conditions

The housing conditions, an important environmental factor for a child's development, comprise several aspects such as type of dwelling, living density and access to modern conveniences. These will first be analysed separately (Table 1 and 2) and then weighted to give a combined housing score.

Type of dwelling

Table 1 shows that more than 90 [illegible] of the families lived in rented flats, which reflects the general trend in Swedish towns [8]. During the children's first 3 years of life there was a small shift toward living in a two-family or one-family house.

Originally some newly established families ($n = [illegible]$) lived in dwellings belonging to near relatives, especially the mother's parents (Table 20). The main cause has probably been the housing shortage in Sweden. Within 3 years all families but one had succeeded in obtaining their own dwellings.

Dwelling space

As regards dwelling space there is a clear tendency to improvement during the children's first 3 years of life. This improvement took place despite the increase in size of the family through the birth of siblings in 40 cases. The improved standard is probably due to the difficulty young families have in getting suitable dwellings in the early years of marriage as well as to the housing policy of the community, which assist families with children.

TABLE 2 *Housing conveniences*

	Age of children							
	At birth (212)		1 year (=211)		2 years (=201)		3 years (204)	
				%	n	%	n	%
Central heating	166	79	165	86	167	83	172	85
Tile stove and/or iron stove (oil coke, electricity)	44	21	43	20	34	17	34	17
Hot water and bathroom	143	67	162	73	154	77	163	79
Hot water no bath	14	7	3	1	5	2	3	1
Cold water supply	50	24	44	21	[illegible]	19	37	18
X water supply	6	3	5	3	3	2	3	1
Own W C	180	85	185	88	180	90	187	91
Shared W C or earth closet	8	4	8	4	8	4	6	3
Earth closet outside of the house	24	11	[illegible]	9	12	6	[illegible]	6

The figures show that dwelling space is very restricted When the mothers came home from the maternity hospital, nearly one third of the families had to live in dwellings with or more persons per room (T ble 1)

When the children were 1 year old 22 of the families still lived in these restricted conditions In these calculations the word room is understood to mean also a kitchen provided t is large enough to sit, eat or sleep in (Practically 100 per cent of the household have their own kit hens at birth of the children 96 , at 1 and 2 years of ge 98 , at 3 years of age 99 5)

The high incidence f restricted dw lling spac is not unique phenomenon for our f milies The same is found in Swedish fficial housing invest gations [8] In a recent socio-psychological study by Jonsson nd K lvesten [6] of a random sample of fam lies w th boy of school-age in Stockholm ** were living in restricted dwel ling space They used a criterion of over crowding more than persons per room This is the generally used norm in Sweden [ ] In these calculations, however the k tchen not included separat room

If this norm for overcrowding is applied to our study at the birth of the children and on their first and third birthdays, then the percentage of overcrowding is more striking 51 43 and 28 per cent respectively When comparing these results t should be borne in mind that Jonsson-Kälvesten s investigations deal with chil dren of school-age and that in our families there is a tendency to less restricted dwel ling space with increasing age of the chil dren

The vercrowding of the families with small children is indeed conspicuous.

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	At birth (n = 21[illegible])		Age of children: 1 year (n = 211)		2 years ([illegible])		3 years ([illegible])	
	n	%	n	%	n	%	n	%
Rented flat	199	91	195	91	184	9[illegible]	16[illegible]	91
Two-family house	–	–	–	–	–	4	3	1
One family house	6		6	[illegible]	10		16	6
1 room	3	1	1	0.4	0	0	0	0
2 rooms	63	[illegible]9	64	[illegible]0	48	[illegible]	3[illegible]	18
3 rooms	6[illegible]	[illegible]6	63	[illegible]9	[illegible]6	9	[illegible]6	[illegible]
4 rooms	2[illegible]	1	50	[illegible]	5[illegible]	[illegible]5	5[illegible]	[illegible]5
[illegible] rooms	13	6	10		11	[illegible]	23	11
> 5 rooms	[illegible]		3	1	[illegible]		11	5
Up to ½ room/person	64	[illegible]0	46	[illegible]	36	18	[illegible]	1
Up to ¾ room/person	63	[illegible]9	86	41	[illegible]9	39	[illegible]	[illegible]
Up to 1 room/person	5[illegible]		60	28	66	[illegible]	[illegible]	37
> 1 room/person	13	6	19	9	[illegible]	10	2[illegible]	1
Separate room for children	26	1	3[illegible]	17	39	19	[illegible]0	[illegible]
Separate room for children only at night	14		14		23	11	14	
No separate room for children	1[illegible]	81	16[illegible]		139	69	122	9

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The housing conditions, an important environmental factor for a child's development, comprise several aspects, such as type of dwelling, living density and access to modern conveniences. These will first be analysed separately (Table 1 and 2) and then weighted to give a combined housing score.

Type of dwelling

Table 1 shows that more than 90 % of the families lived in rented flats, which reflects the general trend in Swedish towns [8]. During the children's first 3 years of life there was a small shift towards living in a two-family or one-family house.

Originally some newly established families (n = 7) lived in dwellings belonging to near relatives, especially the mother's parents (Table 20). The main cause has probably been the housing shortage in Sweden. Within 3 years all families but one had succeeded in obtaining their own dwellings.

Dwelling space

As regards dwelling space there is a clear tendency to improvement during the children's first 3 years of life. This improvement took place despite the increase in size of the family through the birth of siblings in 49 cases. The improved standard is probably due to the difficulty young families have in getting suitable dwellings in the early years of marriage as well as to the housing policy of the community, which assists families with children.

TABLE Housing conveniences

	Age of children							
	At birth (n = 212)		1 year (n 211)		2 years (= 201)		3 years (= 206)	
		%		%	n	%	n	%
Central heating	168	79	168	80	167	83	172	83
Tile stove and/or iron stove (oil coke, electricity)	44	21	43	20	34	17	34	17
Hot water and bathroom	143	67	153	73	154	77	163	79
Hot water no bath	14	7	9	4	5	3	2	1
Cold water supply	50	24	44	[illegible]	39	19	37	18
No water supply	6	3	5	2	2	1	3	1
Own W.C	180	85	185	88	180	90	187	91
Shared W C. or earth closet	8	4	8	4	8	4	6	3
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When the children were 1 year old, 22 of the families still lived in these restricted conditions. In these calculations the word room is understood to mean also a kitchen provided it is large enough to sit eat or sleep in (Practically 100 per cent of the household have their own kitchens t birth of the children 96 at 1 nd years of ge 98 t 3 years of age 99.5 .)

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Access to modern conveniences

We have taken account of the following conveniences: heating system water supply bath and W C. (Table) Fairly modern flats, i.e. with central heating hot water bathroom and W.C., are the domi-

nant type. 67 per cent of the flats fulfilled these conditions at the children's birth and 79 per cent of the families had entirely modern flats when the children were 3 years old Improvements in the housing standards can thus be observed not only in the greater living space but also in access to modern conveniences Our figures for housing conveniences especially when the children are 3 years old are in good agreement with the 1960 conditions in Stockholm [8]

The housing conditions for the studied families may be characterized in short by a high incidence of restricted dwelling space but by a high incidence also of access to modern conveniences

An overall evaluation of the housing quality

In a study of this kind it would be convenient to have a grouping system for overall housing quality This is unfortunately not possible by means of a simple formula which moreover should be applicable also for international comparisons To some extent we can express restricted dwelling space in numerical terms, and we can state the extent to which modern conveniences are available but to balance these magnitudes against each other must involve a certain subjective element In an attempt to evaluate the housing quality we have considered that overcrowding should be given great weight On this account we adapted the Graffar 5-point scale to Swedish conditions using the following minimum requirements

Group		
I	Modern	> 1.5 rooms/person
IIa	Modern	1 0 room/person
IIb	Semi modern	> 1 5 rooms/person
IIIa	Modern	> 0 75 room/person
IIIb	Semi modern	> 1 0 room/person
IVa	Modern	> 0.5 room/person
IVb	Semi modern	> 0 75 room/person
IVc	Unmodern	> 1 0 room/person
Va	Modern	< 0.5 room/person
Vb	Semi modern	< 0 75 room/person
Vc	Unmodern	< 1 0 room/person

In a few cases dwellings near the limit values have been moved into the adjacent group on grounds such as the total number and sizes of the rooms or the age composition of the members of the household. This means that if the density figures are the same the restriction of dwelling space is considered to be greater if a household consists more of adults and older children than of younger children

Here are some typical examples of different categories Group II modern dwellings where the family can use at least one room as a sitting room in addition to the bedrooms An example of the usual dwelling in group III is one with 2 rooms and a good kitchen with all modern conveniences for a family with 2 children. A semi modern flat with the same living space and with the same number of occupants is regarded as belonging to group IV and dwellings which are without either central heating or W C are assigned to group V

Table 3 shows the distribution of the different dwelling groups at the various ages of the children The figures indicate an evident improvement during the 3-year period

By the time the children were 3 years old half of the families (52 of 110) who earlier lived in dwellings classified in groups IV and V had moved to bett r

Modern = central heating W C bathroom
Semi modern one or two of these facilities.
Unmodern = none of these facilities

TABLE 3 *Housing quality*

Classification (according to Graffar)	Age of children: At birth (n = 212) n	%	1 year (n = 212) n	%	2 years (n = 209) n	%	3 years (n = 209) n	%
Group I	5	*2*	8	*9*	6	*3*	10	*5*
Group II	19	*9*	30	*14*	38	*18*	49	*23*
Group III	78	*37*	86	*41*	96	*46*	92	*44*
Group IV	72	*34*	64	*30*	47	*22*	41	*20*
Group V	38	*18*	27	*13*	22	*11*	17	*8*

dwellings but at that age 28 per cent of the children still lived in housing conditions that were unsatisfactory

Parents' Education

With regard to education parents have been classified in the following 5 groups (an adaptation of the Graffar classification to the Swedish school system)

Group		Years of education
I	University examination or equivalent education	15–
II	Matriculation examination ("studentexamen") or similar standard, but not university examination	12–13
III	School certificate ("realexamen") or similar standard, but not matriculation	9–10
IV	Legal obligations relating to school attendance fulfilled (elementary school)	6–8
V	Legal obligations relating to school attendance not fulfilled	

The designation "similar" education covers such vocational training as is given in courses or at training institutes which confer qualifications and the right to apply for posts on a level with those afforded by the corresponding school examinations.

Group II for example, includes the following training schools: technical and commercial colleges, schools for registered nurses and special training colleges for teachers. Group III relates to corresponding schools on a lower level

TABLE 4 *Educational grouping*

Educational category	Father 1 year (n = 212) n	%	Mother 1 year (n = 212) n	%	Family, Age of children: 1 year (n = 212) n	%	2 years (n = 209) n	%	3 years (n = 209) n	%
Group I	26	*12*	3	*1*	27	*13*	24	*11*	26	*12*
Group II	22	*10*	23	*11*	31	*15*	32	*16*	31	*15*
Group III	24	*11*	33	*16*	32	*15*	31	*15*	30	*14*
Group IV	133	*63*	147	*69*	122	*57*	122	*58*	122	*58*
Group V		*0*	1	*0.5*	0	*0*	0	*0*	0	*0*
Unknown	7	*3*	0	*0*	0	*0*	0	*0*	0	*0*

nant type. 67 per cent of the flats fulfilled these conditions at the children's birth and 79 per cent of the families had entirely modern flats when the children were 3 years old. Improvements in the housing standards can thus be observed not only in the greater living space but also in access to modern conveniences. Our figures for housing conveniences, especially when the children are 3 years old, are in good agreement with the 1960 conditions in Stockholm [8].

The housing conditions for the studied families may be characterized, in short, by a high incidence of restricted dwelling space but by a high incidence also of access to modern conveniences.

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In a study of this kind it would be convenient to have a grouping system for overall housing quality. This is unfortunately not possible by means of a simple formula which, moreover, should be applicable also for international comparisons. To some extent we can express restricted dwelling space in numerical terms and we can state the extent to which modern conveniences are available, but to balance these magnitudes against each other must involve a certain subjective element. In an attempt to evaluate the housing quality we have considered that overcrowding should be given great weight. On this account we adapted the Graffar 5-point scale to Swedish conditions using the following minimum requirements:

Group		
I	Modern	> 1 5 rooms/person
II*a*	Modern	> 1 [illegible] room/person
II*b*	Semi modern	> 1 5 rooms/person
III*a*	Modern	> 0 75 room/person
III*b*	Semi modern	> 1 [illegible] room/person
IV*a*	Modern	> 0.5 room/person
IV*b*	Semi modern	> 0.75 room/person
IV*c*	Unmodern	> 1 0 room/person
V*a*	Modern	< 0 [illegible] room/person
V*b*	Semi modern	< 0 75 room/person
V*c*	Unmodern	< 1 0 room/person

Modern – central heating, W C, bathroom.
Semi modern – one or two of these facilities.
Unmodern – none of these facilities.

In a few cases dwellings near the limit values have been moved into the adjacent group on grounds such as the total number and sizes of the rooms or the age composition of the members of the household. This means that if the density figures are the same, the restriction of dwelling space is considered to be greater if a household consists more of adults and older children than of younger children.

Here are some typical examples of different categories. Group II: modern dwellings where the family can use at least one room as a sitting room in addition to the bedrooms. An example of the usual dwelling in group III is one with 2 rooms and a good kitchen with all modern conveniences for a family with 2 children. A semi modern flat with the same living space and with the same number of occupants is regarded as belonging to group IV, and dwellings which are without either central heating or W C are assigned to group V.

Table 8 shows the distribution of the different dwelling groups at the various ages of the children. The figures indicate *an evident improvement during* the 3-year period.

By the time the children were 3 years old, half of the families (of 110) who earlier lived in dwellings classified as groups IV and V had moved to better

TABLE 6. *Permanence of mothers' occupational work*
According to interviews 1, 2 and 3 years after child's birth

	(21?)	% (of 200)
Full time occupation at each investigation	20	10
Either full time or part time at each investigation	9	5
Never any occupational work	117	59
Occupational work on some occasions	54	27
Information lacking for any of the three investigations	12	—

occupational work, for different ages of the child, is distributed between regular and irregular full time and part time employment. Since mother's occupational work is considered a potential factor in the child's development, it is important to point out that none of the mothers had full time occupational work when the child was one month old and 2 months later only 4 per cent of the mothers had started regular occupational work. From 6 months of age up to 3 years there is then a slow gradual increase from 10 to 22 per cent of mothers with regular occupational work.

Mothers who are working "part time irregularly" are those who have casual work, sometimes performed at home at times in the evenings or early mornings. Table 5 shows the occurrence of the mothers' various occupational work at the times when the investigations were carried out, but it does not indicate whether it is the same mothers who are working outside their homes the whole time or not. The permanence of the mothers' occupational work or lack of work is shown in Table 6. During the children's first 3 years of life more than half of the mothers belong to the category of permanent housewives (59 %). Constant full time employment is comparatively rare as long as the children are small (10 %).

Classification of parents' occupations

The Graffar classification system uses five different categories of occupation. It is based on the official British publication, Classification of Occupations (2). The occupations are there grouped as follows:

Group I: professional, etc. occupations
Group II: intermediate occupations
Group III: skilled occupations
Group IV: partly skilled occupations
Group V: unskilled occupations.

This classification has been used for the sake of international comparison [4]. Table 7 gives the distribution of the five categories, for the fathers as well as for the mothers, when the children were 1 year old. When characterizing the occupational category of family the highest of the parents' occupations has been used in accordance with the agreed plan for the international studies. The table also gives the figures for family classification during the first 3 years of life of the children. The real changes, however, are more frequent than this cross-sectional analysis indicates. 16 families went up 1 or 2 categories, 7 families went in the opposite direction. In 9 of the former the change was the result of mothers starting work outside the home; in 4 of the latter group the father had left the family.

During the course of the study, however, it became evident that for several occupa-

TABLE 5 *Mother s occupation*

	Age of children															
	1 month (n = 193)		3 months (n = 194)		6 months (n = 198)		9 months (n = 200)		1[illegible] months (n = 206)		[illegible] months (n = 193)		[illegible] months (n = [illegible]03)		[illegible] mont (= [illegible]9)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Full time regular	0	*0*	3	*2*	1	*9*	6	*13*	28	*14*	[illegible]6	*14*	[illegible]9	*14*	30	*1[illegible]*
irregular	0	*0*	0	*0*	0	*0*	4		6	*3*		*4*	3		10	*[illegible]*
Part time regular	1	*0 5*	4		3		6	*3*	9	*4*	11	*6*	13	*6*	13	*[illegible]*
irregular	0	*0*		*1*	10	*5*	10	*5*	8	*4*	10	*5*	9	*4*	[illegible]	*[illegible]*
No occupational work	194	*99.5*	185	*96*	168	*85*	154	*7*	155	*5*	139	*2*	149	*73*	146	*[illegible]*

Table 4 shows the distribution of the fathers mothers and families educational level If the parents educational levels differ the highest has been taken as representative of the family Only one mother has been assigned to group V She went to school only for 2 years due to illness of long duration Only 1/3 of the fathers and about 1/3 of the mothers received education above legal obligations Of the fathers who reached the matriculation examination the majority went on to university or equivalent education but only 3 of the mothers It is difficult to find suitable material for comparison partly because the educational level in Sweden is rapidly changing nowadays with the changing school system

The nearest adequate material for comparison seems to be Härnquist s [5] investigation of the reserves for higher education This material comprises about 10 000 males born between *1928–1936* The fathers in our sample are on average 5 years older but about half of them were born during that period

According to Härnquist 65 of his material (from towns with university) had passed only elementary school Our corresponding figure is 63 Otherwise we cannot compare our figures for the other categories because we have not subdivided them in quite the same way For the higher educational levels comparisons between the two materials will be inadequate also for the reason that the men in Härnquist s material were followed up only until the age of about 20 years.

As expected there have been few changes in the parents education during the children s first 3 years of life

Although this eductional classification seems to be acceptable from a Swedish point of view it cannot be considered to be directly comparable with that of another country due to differences in school system

Parents Occupation

Frequency of maternal occupation

When describing a child s environment in respect of its parents occupation the first aspect we have considered is whether *the mother has occupational work or not* For further elucidation of this question the data given in the social form have been supplemented by information obtained at the psychological interviews when mothers were asked in detail about their work Occupational work is here defined as paid employment usually performed outside the home Table 5 shows how the mother s

TABLE 6. *Permanence of mothers' occupational work*

According to interviews 1, 2 and 3 years after child' birth

	n (212)	% (of 200)
Full time occupation at each investigation	20	10
Either full time or part time at each investigation	9	5
Never any occupational work	117	58
Occupational work on some occasions	54	27
Information lacking for any of the three investigations	12	—

occupational work for different ages of the child, is distributed between regular and irregular full-time and part-time employment. Since mothers' occupational work is considered as an essential factor in the child's development it is important to point out that none of the mothers had full-time occupational work when the child was one month old, and 2 months later only 4 per cent of the mothers had started regular occupational work. From 6 months of age up to 3 years there is then a slow gradual increase from 10 to 22 per cent of mothers with regular occupational work.

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During the course of the study, however, it became evident that for several occupa-

TABLE 5 *Mother s occupation*

	Age of children															
	1 month (n = 195)		3 months (n = 194)		6 months (n = 198)		9 months (n = *00)		1* months (n = *06)		18 months (n = 193)		4 months (n = *03)		36 months (*03	
	n	%	n	%	n	%	n	%	n	%	n		n			
F ll time regula	0	*0*	3	*2*	17	*9*	6	*13*	8	*14*	6	*14*	29	*14*	[illegible]	[illegible]
irregular	0	*0*	0	*0*	0	*0*	4		6	*3*		*4*	3		10	[illegible]
Part time regula	1	[illegible] *5*	4		3		6	*3*	9	*4*	11	*6*	13	*6*	13	[illegible]
irregular	0	*0*	2	*1*	10	*5*	10	*5*	8	*4*	10	*5*	9	*4*	6	[illegible]
No occupational work	*194*	*99 5*	*185*	*96*	*168*	*85*	*154*	*7*	*165*	*75*	*159*	*7*	*149*	*3*	*146*	

Table 4 shows the distribution of the fathers mothers and families educational level If the parents educational levels differ the highest has been taken as representative of the family Only one mother has been assigned to group V She went to school only for 2 years due to illness of long duration Only 1/3 of the fathers and about 1/3 of the mothers received education above legal obligations Of the fathers who reached the matriculation examination the majority went on to university or equivalent education but only 3 of the mothers. It is difficult to find suitable material for comparison partly because the educational level in Sweden is rapidly changing nowadays with the changing school system

The nearest adequate material for comparison seems to be Härnquist s [5] investigation of the reserves for higher education This material comprises about 10 000 males born between 19?8–1936 The fathers in our sample are on average 5 years older but about half of them were born during that period

According to Harnquist 65 % of his material (from towns with university) had passed only elementary school Our corresponding figure is 63 Otherwise we can not compare our figures for the other categories because we have not subdivided them in quite the same way For the higher educational levels comparisons between the two materials will be inadequate also for the reason that the men in Härnquist s material were followed up only until the age of about 20 years.

As expected there have been few changes in the parents education during the children s first 3 years of life

Although this eductional classification seems to be acceptable from a Swedish point of view it cannot be considered to be directly comparable with that of an other country due to differences in school system

Parents Occupation

Frequency of maternal occupation

When describing a child s environment in respect of its parents occupation the first aspect we have considered is whether the mother has occupational work or not For further elucidation of this question the data given in the social form have been supplemented by information obtained at the psychological interviews when mothers were asked in detail about their work Occupational work is here defined as paid employment usually performed outside the home Table 5 shows how the mother s

TABLE 6 *Permanence of mothers' occupational work*
According to interviews 1, 2 and 3 years after child's birth

	(212)	% (of 200)
Full-time occupation at each investigation	20	10
Either full time or part time at each investigation	9	5
Never any occupational work	117	59
Occupational work on some occasions	54	27
Information lacking for any of the three investigations	12	—

occupational work for different ages of the child, is distributed between regular and irregular full-time and part-time employment. Since mother's occupational work is considered as an essential factor in the child's development, it is important to point out that none of the mothers had full-time occupational work when the child was one month old, and 3 months later only 4 per cent of the mothers had started regular occupational work. From 6 months of age up to 3 years there is then a slow gradual increase from 10 to 22 per cent of mothers with regular occupational work.

Mothers who are working part time irregularly are those who have casual work, sometimes performed at home at times in the evenings or early mornings. Table 5 shows the occurrence of the mothers' various occupational work at the times when the investigations were carried out, but it does not indicate whether it is the same mothers who are working outside their homes the whole time or not. The permanence of the mothers' occupational work or lack of work is shown in Table 6. During the children's first 3 years of life more than half of the mothers belong to the category of permanent housewives (59 %). Constant full-time employment is comparatively rare as long as the children are small (10 %).

Classification of parents' occupations

The Grallar classification system uses five different categories of occupation. It is based on the official British publication Classification of Occupations (..). The occupations are there grouped as follows:

Group I professional, etc. occupations
Group II intermediate occupations
Group III skilled occupations
Group IV partly skilled occupations
Group V unskilled occupations.

This classification has been used for the sake of international comparison [4]. Table 7 gives the distribution of the five categories, for the fathers as well as for the mothers, when the children were 1 year old. When characterizing the occupational category of family the highest of the parents' occupations has been used in accordance with the agreed plan for the international studies. The table also gives the figures for family classification during the first 3 years of life of the children. The real changes however are more frequent than this cross-sectional analysis indicates. 16 families went up 1 or 2 categories, 7 families went in the opposite direction. In 9 of the former the change was the result of mothers starting work outside the home; in 2 of the latter group the father had left the family.

During the course of the study, however, it became evident that for several occupa-

TABLE 7 *Parents occupation (British original)*

	Father		Mother		Family Age of children					
	1 year (n = [illegible]12)		1 year (n = 211)		1 year (n = 21[illegible])		[illegible] years (n = 209)		3 years (n = [illegible]09)	
	n	%	n	%	n	%	n	%	n	%
Group I	[illegible]8	13	2	0	[illegible]8	13	[illegible]7	13	[illegible]	13
Group II	26	12	6	3	30	14	31	15	33	16
Group III	121	57	30	14	1[illegible]6	59	1[illegible]	59	1[illegible]0	57
Group IV	17	8	2	1	17	8	15	7	17	8
Group V	10	5	3	1	11	5	13	6	11	5
No information broken contact with father	7	3								
No occupational work on account of alcoholism	1	0.4								
No occupational work, studying	–	1								
No occupational work, housewife			168*	80						

* These figures include some mothers with part time irregular work or work at home.

tions the placing according to the official British list is not in agreement with common social evaluation in Sweden. There are four kinds of occupations among our studied families which seem to us to be placed too low and two kinds of occupations too high. According to the British system an airline pilot and a navigating officer are classified in group III. According to Swedish conditions they should be in groups I and II respectively. Before their appointment to the civil airline the two men had been respectively an officer in the air force and a graduate engineer and would then have been classified under group I in the British system. As civil aviators their social position in the British system would drop to the same level as skilled workers, locomotive, tram and truck drivers (group III).

Under the British system there is no differentiation between different kinds of teachers (group II) such as secondary school and elementary school teachers. In Sweden the former are trained at university and the latter at special training colleges. It is thus reasonable to place the former in the same group (I) as occupations requiring a university education of corresponding duration. For the same reason a veterinary surgeon should be placed in group I instead of group II.

A differentiation between engineers of higher and lower degree seems also to be justified. They generally attain positions of different responsibility correlated to their degree. In the British system, however, they all belong to group I. Engineers who have not studied technology at a university level should be placed in group II. Furthermore, it is strange to us to find drivers of trams, busses, taxi cabs and trucks on the same level as skilled workers who have required a relatively long period of training (group III). We consider the former to belong rather to the group of partly skilled workers (group IV).

If the British classification is modified

TABLE 8. *Parents' occupation (British modified)*

	Age of children					
	1 year (= 212)		2 years (= 209)		3 years (= 209)	
	n	%	n	%		%
Group I	24	11	[illegible]	11	[illegible]	11
Group II	36	17	[illegible]	18	40	19
Group III	106	50	106	51	101	48
Group IV	35	17	31	15	33	16
Group V	11	5	[illegible]	6	12	6

in this way the classification changes in 32 cases out of 212 (i.e. 15 %).

Table 8 shows how the families are distributed over the different occupational categories after these modifications

Family Income

Income obviously is an essential factor in family's living arrangements. In planning for the internationally coordinated studies, however, it was considered impossible for some of the participating study groups to obtain information on income. Therefore Graffar introduced as one of his five criteria the more easily ascertained criterion, main source of family revenue. In America Warner (12) has found this criterion closely related to the amount of family revenue. Graffar divides the sources of family revenue into five groups.

Group I: persons whose income is derived from private property

Group II. persons who are self-employed or engaged in independent professions and whose income consists in perquisites, profits or fees

Group III: employees receiving a monthly salary

Group IV: employees or casual labourers receiving wages weekly or daily

Group V: persons who are in receipt of public or private relief of more permanent nature. (This does not include assistance received through sickness or unemployment insurance; in such cases group classification depends upon the manner in which the income is earned under normal conditions.)

On this basis the classification is shown in Table 9

Source or revenue has turned out to be a less suitable variable for Swedish conditions. First, we do not find the close relation between source of revenue and amount of family income (Table 1*) as reported by Warner [1*]. On the contrary the correlation between the two variables is only .19 which is much lower than any other correlation between the social grouping variables (see also page 40 where the interrelation between several variables is discussed). Secondly the material is distributed mainly among the three middle categories.

We have considered the taxable income to be a better measure of financial status.

It has been possible to obtain this information in 98 % of the families, and we shall thus use it as an alternative to source of income.

We have set the limits for the income groups at 5000, 10,000, 18 000 and 30,000 Swedish crowns. On account of changes in monetary value during the years of

TABLE 9. *Main source of family income*

	Age of children					
	1 year (n = 212)		2 years (= 209)		3 years (= 209)	
	n	%	n	%	n	%
Group I	0	0	0	0	0	0
Group II	12	6	12	6	12	6
Group III	133	63	124	59	124	59
Group IV	65	31	70	33	70	33
Group V	1	0.5	2	1	2	1

TABLE 7 *Parents occupation (British original)*

	Father		Mother		Family Age of children					
	1 year (n = 212)		1 year (n = [illegible]11)		1 year (n = 21[illegible])		[illegible] years (n = [illegible]00)		3 years (n = [illegible]00)	
	n	%	n	%	n	%	n	%	n	%
Group I	28	*13*		*0*	[illegible]8	*13*	27	*13*	[illegible]8	*13*
Group II	26	*12*	6	*3*	30	*14*	31	*15*	33	*16*
Group III	121	*57*	30	*14*	1[illegible]6	*59*	1[illegible]3	*59*	1[illegible]0	*57*
Group IV	17	*8*	2	*1*	17	*8*	15	*7*	17	*8*
Group V	10	*5*	3	*1*	11	*5*	[illegible]	*6*	11	*5*
No information broken contact with father	7	*3*								
N occupational work on account of alcoholism	1	*0 4*								
No occupational work, studying	2	*1*								
No occupational work housewife			168*	*80*						

These figures include some mothers with part time irregular work or work t home.

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Under the *British system there is no* differentiation between different kinds of teachers (group *II*) *such as secondary* school and elementary school teachers. In *Sweden the former are trained at* univer sity and the latter at special training colleges *It is thus reasonable to place the* former in the same group (I) as occupa *tions requiring a university* education of corresponding duration For the same rea son a veterinary surgeon should be placed in group I instead of group II

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If the British classification is modified

TABLE 8. *Parents occupation* (British modified)

	Age of children					
	1 year (n = 212)		2 years (n = 209)		3 years (n = 209)	
	n	%	n	%	n	%
Group I	24	11	23	11	23	11
Group II	36	17	37	18	40	19
Group III	106	50	106	51	101	48
Group IV	35	17	31	15	33	16
Group V	11	5	13	6	12	6

In this way the classification changes in 32 cases out of 212 (i.e. 15 %).

Table 8 shows how the families are distributed over the different occupational categories after these modifications.

Family Income

Income, obviously is an essential factor in a family's living arrangements. In planning for the internationally coordinated studies, however, it was considered impossible for some of the participating study groups to obtain information on income. Therefore Graffar introduced as one of his five criteria the more easily ascertained criterion, main source of family revenue. In America Warner (12) has found this criterion closely related to the amount of family revenue. Graffar divides the sources of family revenue into five groups:

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Group IV employees or casual labourers receiving wages weekly or daily

Group V persons who are in receipt of public or private relief of a more permanent nature (This does not include assistance received through sickness or unemployment insurance in such cases group classification depends upon the manner in which the income is earned under normal conditions.)

On this basis the classification is shown in Table 9.

Source or revenue has turned out to be a less suitable variable for Swedish conditions. First we do not find the close relation between source of revenue and amount of family income (Table 12) as reported by Warner (12). On the contrary the correlation between the two variables is only 19 which is much lower than any other correlation between the social grouping variables (see also page 40 where the interrelation between several variables is discussed). Secondly the material is distributed mainly among the three middle categories.

We have considered the taxable income to be a better measure of financial status.

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We have set the limits for the income groups at 5000 10 000 15,000 and 30 000 Swedish crowns. On account of changes in monetary value during the years of

TABLE 9. *Main source of family income*

	Age of children					
	1 year (n = 212)		2 years (n = 209)		3 years (n = 209)	
	n	%	n	%	n	%
Group I	0	0	0	0	0	0
Group II	13	6	12	6	13	6
Group III	133	63	124	59	124	59
Group IV	65	31	70	33	70	33
Group V	1	0.5	3	1	2	1

TABLE 7 *Parents occupation (British original)*

	Father		Mother		Family Age of children					
	1 year (n = [illegible]12)		1 year (n = 211)		1 year (n = 212)		[illegible] years (n = [illegible]09)		3 years (n = [illegible]09)	
	n	%	n	%	n	%	n	%	n	%
Group I	6	*13*	[illegible]	*0*	8	*13*	7	*13*	[illegible]8	*13*
Group II	[illegible]6	*12*	6	*3*	30	*14*	31	*15*	[illegible]	*16*
Group III	1[illegible]1	*57*	30	*14*	1[illegible]8	*59*	1[illegible]	*59*	1[illegible]0	*57*
Group IV	17	*8*		*1*	17	*8*	15	*7*	17	*8*
Group V	10	*5*	3	*1*	11	*5*	13	*6*	11	*5*
No information broken contact with father	7	*3*								
No occupational work on account of alcoholism	1	*0 4*								
No occupational work, studying	2	*1*								
No occupational work, housewife			168*	*80*						

These figures include some mothers with part time irregular work or work at home

tions the placing according to the official British list is not in agreement with common social evaluation in Sweden There are four kinds of occupations among our studied families which seem to us to be placed too low and two kinds of occupations too high According to the British system an airline pilot and a navigating officer are classified in group III According to Swedish conditions they should be in groups I and II respectively Before their appointment to the civil airline the two men had been respectively an officer in the air force and a graduate engineer and would then have been classified under group I in the British system As civil aviators their social position in the British system would drop to the same level as skilled workers locomotive tram and truck drivers (group III)

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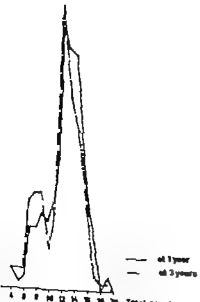
If the British classification is modified

TABLE 11. *Social grouping*

	Age of children					
	1 year (= 212)		2 years (= 209)[a]		3 years (= 209)[a]	
	n	%	n	%	n	%
Swedish system						
Group I	35	*17*	32	*15*	32	*15*
Group II	79	*37*	84	*40*	84	*40*
Group III	98	[illegible]	93	*44*	93	*44*
Graffar scale						
Class I	9	*4*	10	*5*	12	*6*
Class II	44	*21*	42	*20*	44	[illegible]
Class III	[illegible]	*30*	73	*35*	70	*34*
Class IV	86	*41*	74	*35*	74	*35*
Class V	9	*4*	10	*5*	9	*4*
Modified scale	(= 208)		(= 208)		(= 208)	
Class I	[illegible]	*7*	16	*8*	22	*11*
Class II	30	*14*	33	*16*	34	*17*
Class III	70	*34*	78	*38*	70	*34*
Class IV	84	*40*	74	*36*	[illegible]	[illegible]
Class V	9	*4*	7	*3*	4	*2*

[a] The three children lost from the study belonged to group I.



1. Modified total score at 1 year (= 208) and 3 years (200).

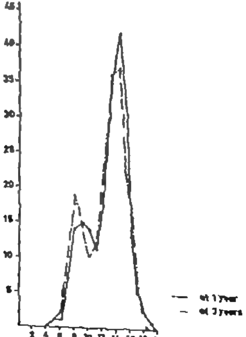


Fig. 2. Graffar total score at 1 year (n = 212) and 3 years (= 209).

TABLE 10 *Taxable income*

	Age of children					
	1 year (n = 208)		2 years (n = 208)		3 years (n = 203)	
	n	%	n	%	n	%
Group I > 30 000	3	*1*	4	*2*	5	*2*
Group II 18–30 000	24	*12*	30	*14*	48	*23*
Group III 10–18.000	129	*62*	131	*63*	111	*54*
Group IV 5–10.000	44	*21*	31	*15*	3	*16*
Group V < 5 000	8	*4*	12	*6*	9	*4*

study the nominal values have been adjusted to the level of the year 1955 according to the consumer price index issued by the Swedish Social Welfare Board. The distribution of family incomes during the children s first three years of life are shown in Table 10

As expected this variable has a better distribution over the whole range of the income scale

Social Grouping

In the preceding pages we have presented several variables each of which describes one aspect of the social situation of a family In many instances it is more convenient and practical to have if possible some kind of measure which sums up the total social situation even if this method has some disadvantages [1]

In Sweden the most commonly used social grouping is a division into three categories (Table 11) This is mainly based on a grouping of occupations It crudely differentiates between upper middle and working classes

For the international investigation of which this study is a part Graffar [3] has developed a socio-economic classification including the following variables

1) dwelling 2) occupation, 3) education 4) source of revenue 5) type of district inhabitated The fifth variable has been impossible for us to use, so we have excluded it (in accordance with Graffar s instructions) By adding the figures of the different variables for each family one obtains the total figure indicating the socio-economic level of the family As the range in each variable is 1 5 the variability of the total score is from 4 to 20 (when the fifth variable is excluded) This scale will be referred to as Graffar total score Graffar has also combined the 16 degrees of the scale into 5 social classes in the following way·

Total score 4–7 = social class I
Total score 8–10 = social class II
Total score 11–13 = social class III
Total score 14–16 = social class IV
Total score 17–20 = social class V

In the previous pages we have discussed some inadequacies when adapting this system to Swedish conditions This holds mainly for the two variables "grouping of occupations and „source of revenue By introducing the earlier mentioned modifications in the grouping of occupations and by replacing source of revenue by amount of income and by excluding district in

TABLE 13. *Changes in social group variables from 1–3 years*

Variable	Number of families moved to (a) higher group	(b) lower group
British occupation	16	7
Modified occupation	16	7
Education	4	1
Source of revenue	0	15
Income grouping	58	16
Dwelling	57	14
Social class (according to Graffar)	36	10
Social class ("modified")	48	6
Social group (Swedish system)	10	5

parently because both differentiat labourers from other employees.

The correlation coefficients are higher for the modified occupation scale than for the original one.

Generally it may be said that none of the correlations are so high as to justify exclusion of any one of the variables. Each of them seems to contribute a rather large portion of specific variance so that a combined scale might give a rather good overall measure of the social status of a family.

Changes in Social Conditions During the First Three Years

When describing the different social variables, we have pointed out the changes that have occurred during the period. In Table 13 the data are summed up to give an overall view of the changes up to three years. There is a distinct trend towards improvement of the social conditions during the period. This is evident particularly as regards income and dwelling, whereas educational standard usually does not change. The improvement of the social conditions is recognized also in a shift towards higher social class in many families. In the modified social class scoring, 48 families moved to a higher group and only 6 families to a lower one. Only in 65 families were no changes whatsoever registered during the period.

These changes probably reflect a development towards the stabilization of the social status of the youngest families as well as the general increase of social standard in Sweden during these years.

Family Data

The family situation of the children will be described by the following family data: age of parents, completeness of family

TABLE 14. *Parents' age at children's birth*

years	16–19 n	%	20–24 n	%	25–29 n	%	30–34 n	%	35–39 n	%	40–44 n	%	45–49 n	%	50– n	%
Mothers age	11	*5*	49	*22*	72	*34*	46	*22*	20	*9*	4	*2*				
Fathers age	3	*1*	30	*14*	81	*38*	47	*22*	34	*16*	11	*6*	3	*1*	3	*1*

TABLE 12 *Coefficients of correlation of social grouping variables (when the children are 3 years old)*

	Modified occupation	Families education	Source of revenue	Income	Dwelling	Graffar social class	Modified social class
British occupation	89	66	48	.33	4.	79	
Modified occupation		73	.51	39	.51	[illegible]	83
Families education			.37	4	4	79	.83
Source of revenue				19	35	65	45
Income					.39	43	6.
Dwelling						70	71
Graffar social class							87

habited we have obtained a modified total score and modified social class

We shall use the original Graffar system mainly for international comparisons. Table 11 shows the distribution of our families in the different social grouping systems.

The different variables of Graffar's original and our modified social grouping system are all with the exception of educational level approximately normally distributed during the years under consideration The modified scales seem to be somewhat better than the original ones also in this respect

Concerning the two versions of total score a tendency towards bimodal distribution can be observed in the present material (Figs 1 and 2) In the original Graffar scale the bimodality is present already when the children are 1 year old, while in the modified scale it seems to be a gradually developing process in this direction The division line is at circa 10 points at 3 years which separates out the *roughly* 25 % having the best social conditions.

Intercorrelations Between Different Social Variables

It is neither meaningful nor possible to give a complete report of all the different relations between the social variables here but we may consider a few important intercorrelations.

Table 12 shows the intercorrelations between the variables belonging to the original and the modified Graffar socio-*economic scales*[1]

Note the extremely low correlation between the two variables which are supposed to measure the family's economic standard. It is only 19 and thus a good deal lower than any other correlation in the matrix On the whole moreover the two measures of income show a rather low correlation to the other variables *Source of revenue* however correlates rather well with occupation (48 with the original and .51 with the modified) ap-

[1] The original Graffar scale consist of British Occupation Education, Source of Revenue Dwelling Our modified scal consist of Modified Occupation, Education Income and Dwelling

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The family situation of the children will be described by the following family data age of parents, completeness of family

TABLE 14 *Parents' age at children's birth*

years	15–19 n	%	20–24 n	%	25–29 n	%	30–34 n	%	35–39 n	%	40–44 n	%	45–49 n	%	50– n	%
Mothers age	11	5	56	28	[illegible]	34	48	22	20	9	4	2				
Fathers age	2	1	30	14	81	38	47	22	34	16	13	6	3	1	2	1

TABLE 12 *Coefficients of correlation of social grouping variables (when the children are 3 years old)*

	Modified occupation	Families education	Source of revenue	Income	Dwelling	Graffar social class	Modified social class
British occupation	89	66	48	.33	43	79	
Modified occupation		[illegible]	.51	.39	.51	.83	83
Families education			37	42	4	70	83
Source of revenue				19	35	65	45
Income					.39	43	[illegible]
Dwelling						0	71
Graffar social class							87

habited we have obtained a modified total score and modified social class

We shall use the original Graffar system mainly for international comparisons Table 11 shows the distribution of our families in the different social grouping systems

The different variables of Graffar s original and our modified social grouping system are all with the exception of educational level approximately normally distributed during the years under consideration. The modified scales seem to be somewhat better than the original ones also in this respect

Concerning the two versions of "total score a tendency towards bimodal distribution can be observed in the present material (Figs 1 and 2) In the original Graffar scale the bimodality is present already when the children are 1 year old while in the modified scale it seems to be a gradually developing process in this direction The division line is at circa 10 points at 3 years, which separates out the roughly 25 % having the best social conditions.

Intercorrelations Between Different Social Variables

It is neither meaningful nor possible to give a complete report of all the different relations between the social variables here but we may consider a few important intercorrelations

Table 12 shows the intercorrelations between the variables belonging to the original and the modified Graffar socio-economic scales.[1]

Note the extremely low correlation between the two variables which are supposed to measure the family s economic standard It is only 19 and thus a good deal lower than any other correlation in the matrix On the whole moreover the two measures of income show a rather low correlation to the other variables. Source of revenue however correlates rather well with occupation (48 with the original and .51 with the modified) ap-

[1] The original Graffar scale consist of British Occupation, Education, Source of Revenue Dwelling Our modified scale consist of Modified Occupation, Education, Income and Dwelling

TABLE 13 *Changes in social group variables from 1–3 years*

Variable	Number of families moved t (a) higher group	(b) lower group
British occupation	16	7
Modified occupation	16	7
Education	4	1
Source of revenue	9	18
Income grouping	55	19
Dwelling	57	14
Social class (according to Graffar)	36	10
Social class ("modified")	48	6
Social group (Swedish system)	10	5

parently because both differentiate labourers from other employees.

The correlation coefficients are higher for the modified occupation scale than for the original one.

Generally it may be said that none of the correlations are so high as to justify exclusion of any one of the variables. Each of them seems to contribute a rather large portion of specific variance so that a combined scale might give a rather good overall measure of the social status of a family

Changes in Social Conditions During the First Three Years

When describing the different social variables, we have pointed out the changes that have occurred during the period. In Table 13 the data are summed up to give an overall view of the changes up to three years. There is a distinct trend towards improvement of the social conditions during the period. This is evident particularly as regard income and dwelling, whereas educational standard usually does not change The improvement of the social conditions is recognized also in a shift towards higher social class in many families. In the modified social class scoring 48 families moved to a higher group and only 6 families to a lower one Only in 65 families were no changes whatsoever registered during the period.

These changes probably reflect a development towards the stabilization of the social status of the youngest families as well as the general increase of social standard in Sweden during these years

Family Data

The family situation of the children will be described by the following family data. age of parents, completeness of family

TABLE 14. *Parents age at children s birth*

years	15–19 n	%	20–24 n	%	25–29 n	%	30–34 n	%	35–39 n	%	40–44 n	%	45–49 n	%	50– n	%
Mothers age	11	5	50	[illegible]	72	34	48	22	20	9	4	2				
Fathers age	2	1	30	14	81	38	47	22	34	16	12	6	3	1	3	1

TABLE 15 *Parents age at children s birth in different social groups (Swedish grouping system)*

	Social group		
	I (n = 35)	II (n = 79)	III (n = 98)
Mean age of mother	28.8	28.5	6.0
Mean age of father	32.0	31 0	28.8
	t	*P*	
Mean diff			
f r mothers I–II	0 248	—	
I–III	2.577	02	
II–III	3 095	005	
Mean diff			
fo fathers I–II	0 798	—	
I–III	2.464	02	
II III	2.223	05	

civil status of the mother number and order of siblings and other members of the family

Parents age at birth of the child

The age distribution (grouped in 5-year intervals) for the mothers and fathers is given in Table 14 Compared with available figures for the population of Stockholm and Sweden respectively there is good agreement though with a slight tendency towards younger ages in our families

The father is some years older than the mother which shows the same trend as in the Swedish population as a whole The mean age of the mothers was at the children s birth 27 4 years and the range 15–42 years. Corresponding figures for the fathers were 30 1 years and 19–54 years

As evident from Table 15 there are significant differences in mean age both for fathers and mothers between the lowest social group (Swedish group III) on the one hand and the higher groups (Swedish I + II) on the other In the two latter groups the parents are about 2 3 years older

Completeness of the families

89 % (n = 189) of the children in the sample were born in wedlock (of these, 24 % during the first 8 months of the marriage) The remaining 11 % were born out of wedlock.

When evaluating the family situation it is important to recognize that some of the unmarried mothers were living with the child s father under conditions resembling marriage From the child s point of view such family like conditions may be considered similar to those of a child whose parents are formally married This is especially true when the parents get married later as happened in 9 out of the 16 incidences within 3 years after the child s birth. Four couples continued to live together without being married For the remaining 3 children the parents separated

TABLE 16 *Birth in relation to time of wedlock in different social groupings and variables*

		A – out of wedlock (n = 23)		B – within 8 months of marriage (= 48)		C – after 8 months f marriage (n = 144)	
		n	%	n	%	n	%
Social groups							
Swedish social group	I	0	*0*	4	*9*	[illegible]	*23*
	II	6	*26*	15	*33*	[illegible]	*40*
	III	17	*74*	26	*58*	55	*38*
Gredler social group	I + II	1	*4*	9	*20*	43	*30*
	III	4	*17*	15	*33*	45	*31*
	IV + V	18	*78*	21	*46*	56	*39*
Social variables							
Modified occupation	I + II	0	*0*	9	*20*	51	*36*
	III	[illegible]	*57*	25	*56*	68	*47*
	IV + V	10	*43*	11	*24*	25	*18*
Mother' educational level	I + II	0	*0*	7	*16*	26	*17*
	III	0	*0*	5	*11*	26	*20*
	IV + V	23	*100*	33	[illegible]	90	*63*
Dwelling	I + II	1	*4*	4	*9*	30	*20*
	III	6	*26*	19	*42*	61	*42*
	IV + V	16	*69*	22	*49*	53	*37*
Income	I + II	1	*5*	3	*7*	23	*16*
	III	7	*33*	29	*62*	84	[illegible]
	IV + V	14	*63*	[illegible]	*31*	[illegible]	*17*

during the first 3 years which may be considered as comparable with the situation when a marriage is dissolved.

Even so we have made a comparison of the social status between the following three groups (Tables 16 and 17)

A. The child born out of wedlock
B. The child born within 8 months of marriage
C The child born more than 8 months after marriage

Table 16 shows that children born out of wedlock belong to a greater extent to lower social groupings 3/4 of them to Swedish social group III. The differences between the groups A and C are statistical significant ($P < 01$)

In group A (born out of wedlock) the parents ages at the children s birth are low and differ significantly from those in group C. The mean ages in group A are 23.7 years for mothers and 25 years for

TABLE 17 *Proportion of children born to unmarried, 8 months and more than 8-months married parents in different social groups*

Swedish social group	A out of wedlock		B – within 8 months of marriage		C after 8 months of marriage		Total
	n	%	n	%	n	%	n
I	0	*0*	4	*11*	21	*60*	35
II	6	*8*	15	*19*	58	*73*	79
III	17	*17*	26	*27*	55	*56*	98

TABLE 15 *Parents age at children s birth in different social groups (Swedish grouping system)*

	Social group		
	I (n = 35)	II (n = 79)	III (n = 98)
Mean age of mother	[illegible]8.8	28.5	[illegible]6.0
Mean age of father	32 0	31 0	[illegible]8.8
	t	*p*	
Mean diff for mothers I–II	[illegible] 48	—	
I–III	2.677	02	
II–III	3.095	005	
Mean diff. for fathers I–II	[illegible] 798	—	
I–III	2.464	02	
II III	2.223	03	

civil status of the mother number and order of siblings and other members of the family

Parents age at birth of the child

The age distribution (grouped in 5-year intervals) for the mothers and fathers is given in Table 14 Compared with avail able figures for the population of Stock holm and Sweden, respectively there is good agreement though with a slight tend ency towards younger ages in our families.

The father is some years older than the mother which shows the same trend as in the Swedish population as a whole The mean age of the mothers was at the chil dren s birth 27 4 years and the range 15–42 years. Corresponding figures for the fathers were 30 1 years and 19–54 years.

As evident from Table 15 there are significant differences in mean age both for fathers and mothers between the lowest social group (Swedish group III) on the one hand and the higher groups (Swedish I+II) on the other In the two latter groups the parents are about 2 3 years older

Completeness of the families

89 % (n = 189) of the children in the sample were born in wedlock (of these, 24 % during the first 8 months of the mar riage) The remaining 11 % were born out of wedlock

When evaluating the family situation it is important to recognize that some of the unmarried mothers were living with the child s father under conditions resembling marriage From the child s point of view such family like conditions may be con sidered similar to those of a child whose parents are formally married This is especially true when the parents get mar ried later as happened in 9 out of the 16 incidences within 3 years after the child s birth Four couples continued to live together without being married. For the remaining 3 children the parents separated

TABLE 16 *Birth in relation to time of wedlock in different social groupings and variables*

		A – out of wedlock (n = 23)		B – within 8 months of marriage (n = 45)		C – after 8 months of marriage (n = 144)	
		n	%	n	%	n	%
Social groups							
Swedish social group	I	0	*0*	4	*9*	31	*22*
	II	6	*26*	16	*33*	56	*40*
	III	17	*74*	26	*48*	55	*38*
Graffar' social group	I + II	1	*4*	9	*20*	43	*30*
	III	4	*17*	15	*33*	45	*31*
	IV + V	18	*78*	21	*46*	56	*39*
Social variables							
Modified occupation	I + II	0	*0*	9	*20*	51	*36*
	III	13	*57*	25	*56*	68	*47*
	IV + V	10	*43*	11	*24*	25	*18*
Mother educational level	I + II	0	*0*	7	*16*	25	*17*
	III	0	*0*	5	*11*	28	*20*
	IV + V	23	*100*	33	*73*	90	*63*
Dwelling	I + II	1	*4*	4	*9*	30	*20*
	III	6	*26*	19	*42*	61	*42*
	IV + V	16	*69*	22	*49*	53	*37*
Income	I + II	1	*5*	3	*7*	23	*16*
	III	7	*32*	28	*62*	94	*67*
	IV + V	14	*63*	14	*31*	24	*17*

during the first 3 years, which may be considered as comparable with the situation when a marriage is dissolved.

Even so, we have made a comparison of the social status between the following three groups (Tables 16 and 17):

A. The child born out of wedlock
B. The child born within 8 months of marriage
C. The child born more than 8 months after marriage

Table 16 shows that children born out of wedlock belong to greater extent to lower social groupings, 3/4 of them to Swedish social group III. The differences between the groups A and C are statistical significant ($P < .01$)

In group A (born out of wedlock) the parents ages at the children's birth are low and differ significantly from those in group C. The mean ages in group A are 23.7 years for mothers and [illegible] years for

TABLE 17 *Proportion of children born to unmarried, 8 months and more than 8 months married parents in different social groups*

Swedish social group	A – out of wedlock		B – within 8 months of marriage		C – after 8 months of marriage		Total
	n	%	n	%	n	%	n
I	0	*0*	4	*11*	31	*89*	35
II	6	*8*	14	*19*	58	*73*	79
III	17	*17*	26	*27*	55	*56*	98

fathers Corresponding figures for group C (conceived in wedlock) are 29 for mothers and 31 9 years for fathers (Table 18)

It is evident that from a social point of view the children born out of wedlock are an unfavoured group a fact to bear in mind in comparisons This holds true also in comparison with group II where the parents ages do not differ significantly from those in group A The ages of parents, then do not seem to be a decisive factor in the differences

The home situation of the 200 children can be summarized as follows.

For 101 children the family was *complete*

181 couples married during the 3-year period
7 couples living together and later married
3 couples living together unmarried

For 13 children the family was *broken up*

6 couples married at birth of child, later divorced
6 couples living together unmarried, later separated (one temporarily married)
1 couple father in inebriates home child in foster home

For 5 children the family was *never complete*

the mother being unmarried and never living with the father of the child. However this very seldom means that the children lived without any other grown ups than theirmother (only 2 children)

For 18 children whose families were *broken up or* had *never* been *complete* the family situation when the children were 3 years old was as follows

4 children in foster homes
3 children in children s home
11 children lived with their mothers, of them ha ing a stepfather

Tables 19 and 20 show the cross-sectional changes of the parents civil status and the children s home situation

Number of children and order of sequence

The average number of children per family is 1 9 at the children s birth.

Table 21 shows the inconsiderable per centual differences in the distribution of children of different birthorder in the various social classes.

49 children got a younger sibling during their first 3 years of life, none more than one 29 of these were firstborns. Table 22 shows the order of birth of the children in relation to number of older as well as *younger siblings*

Total number of members in the household

Table 23 shows the distribution of the sizes of households when the children are 1 2 and 3 years of age At all ages the majority of households consist of 4 persons The natural development towards larger households is reflected in the figures but some of the largest households (6 or more persons) decreased owing to the parents moving away from their relatives when they obtained their own dwelling

Summary

The social conditions of the 212 families participating in the longitudinal study during the children s first three years of life are described with reference to 23 tables and 2 figures in respect of housing standard education occupation and income The material is classified under each of these *variables on a 5-grade scale* in accordance with an international social grouping system (Graffar) The aggregate values of the different variables are considered to reflect the socio-economic level of the family

TABLE 18. *Parents' age for children born out of wedlock, within 8 months and after 8 months of marriage*

	A = out of wedlock	B = within 8 months of marriage	C = after 8 months of marriage
Mean age: Mother	23.7	24	29
Mean age: Father	26	27	31.9

		t	p
Mean diff. for mothers	A–B	0.198	—
	A–C	4.688	001
	B–C	5.961	001
Mean diff. for fathers	A–B	1.607	—
	A–C	4.964	.001
	B–C	4.778	.001

TABLE 19. *Civil status of parents*

	Age of children							
	At birth (n = 212)		1 year (n = 212)		2 years (n = 209)		2 years (n = 209)	
	n	%	n	%	n	%	n	%
Married, living together	189	89	192	91	192	92	190	90
Married, then separated or divorced	0	0	1	0.5	2	1	6	3
Not married, but living together	17	8	13	6	6	3	3	1
Not married, not living together	6	3	6	3	6	3	7	3
Child living in foster-home	0	0	0	0	3	1	4	2

TABLE 20. *The children's home situation*

	Age of children					
	1 year (n = 212)		2 years (n = 209)		3 years (n = 209)	
	n	%	n	%	n	%
With mother (M) + Father	197	93	196	94	191	91
With M + F + relatives	7	3	2	1	1	0.5
With M	3	1	2	1	7	3
With M + relatives	4	2	3	1	2	1
With M + weekday foster parents	0	0	1	0.5	0	0
With M + stepfather	0	0	1	[redacted]	1	0.5
With foster parents	0	0	2	1	4	2
Children's home	1	0.5	2	1	3	1

TABLE 21 *Birth order of children in different social classes*

	1st born		2nd born		3rd born and more		Total
	n	%	*n*	%	*n*	%	*n*
Swedish social group							
I	11	31	18	51	6	17	35
II	8	35	35	44	16	20	79
III	45	46	37	38	[illegible]	16	98
Tot l	84		90		38		21
Graffar social lass							
I + II	20	38	5	47	8	15	53
III	27	4	6	41	11	17	64
IV + V	37	39	39	41	10	20	[illegible]
Total	84		90		38		212

TABLE 22 *Distribution of siblings*

(The twins in three pairs f twins have been given the same successional number)

Number of older sibli gs	Number of children *n*	%	Number f hildren who got a younger sibling:* before 1 yea	between 1 2 years	between 2–3 years	up t 3 years of age
0	84	40	1	16	10	9
1	90	42	1	7	7	15
2	..2	10		1	2	3
3	12	6		1	1	2
4		1				
5	2	1				
Total	1		2	7	20	49

No child got two younger siblings during the first 3 years.

TABLE 23 *Size of the households*

Number of persons	Age of children: 1 year (*n* = 21) *n*	%	2 years (*n* = 201) *n*	%	3 years (*n* = 206) *n*	%
2	[illegible]	*0*	0	*0*	2	*1*
3	69	*33*	56	*28*	40	*24*
4	88	*42*	85	*42*	95	*46*
5	29	*14*	38	*19*	36	*18*
6	[illegible]	*9*	[illegible]	*7*	11	*5*
7	4	*2*	5	*3*	8	*4*
8 and more	3	*1*	3	*2*	2	*1*
In hildren home	1	*0.5*	1	*0.5*	3	*2*

A modification of the international system has been applied that is better adapted to Swedish conditions.

Calculations of the correlations between the different variables and between them and the total social score show no such high coefficients as would justify the exclusion of any variable on that account

A third social classification that has been used is the 3-grade scale based on occupation ı commonly employed in Sweden.

Family data are reported, comprising the age of the mother and father composition of family mother s civil status and time of conception in relation to date of marriage. The incidence of children born out of wedlock was 11 %. Their unfavourable social conditions are demonstrated.

The social status of the entire sample underwent a manifest improvement during the children s first three years of life The main improvement was in the housing standard. An improvement of real income was also noticeable While 5.. per cent of the children lived in unsatisfactory housing condition at birth, the figure was 28 per cent at 3 years of age As regards mother occupation only 15 per cent had half-time or full time employment from one to three years after the child s birth.

In so far as comparisons could be made with adequate official statistics and published studies of social conditions and family data the agreement has been good.

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1 Carlsson G. *Social Mobility and Class Structure* (page 17). Gleerup, Lund, 1958
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TABLE 21 *Birth order of children in different social classes*

	1st born n	%	2nd born n	%	3rd born and more n	%	Total n
Swedish social group							
I	11	31	18	51	6	17	35
II	28	35	35	44	16	20	79
III	45	46	37	38	16	16	98
Total	84		90		38		212
Graffar social class							
I+II	20	38	25	47	8	15	53
III	27	42	26	41	11	17	64
IV+V	37	39	39	41	19	20	95
Total	84		90		38		212

TABLE 22 *Distribution of siblings*

(The twins in three pairs of twins have been given the same successional number)

Number of older siblings	Number of children n	%	Number of children who got a younger sibling: before 1 year	between 1–2 years	between 2 years	up to 3 years of age
0	84	40	1	18	10	29
1	90	42	1		7	15
2	22	10		1		2
3	12	6		1	1	
4	2	1				
5	2	1				
Total	212			7	20	49

No child got two younger siblings during the first 3 years.

TABLE 23 *Size of the households*

Number of persons	Age of children: 1 year (n = 212) n	%	2 years (n = 201) n	%	3 years (n = 206) n	%
2	0	*0*	0	*0*	2	*1*
3	69	*33*	56	*28*	49	*24*
4	88	*42*	85	*42*	95	*46*
5	29	*14*	38	*19*	36	*18*
6	18	*9*	13	*7*	11	*5*
7	4	*2*	5	*3*	8	*4*
8 and more	3	*1*	3	*2*	2	*1*
In children's home	1	*0.5*	1	*0.5*	3	*2*

A modification of the international system has been applied that is better adapted to Swedish conditions.

Calculations of the correlations between the different variables and between them and the total social score show no such high coefficients as would justify the exclusion of any variable on that account.

A third social classification that has been used is the 3-grade scale based on occupation as commonly employed in Sweden.

Family data are reported, comprising the age of the mother and father, composition of family, mother's civil status and time of conception in relation to date of marriage. The incidence of children born out of wedlock was 11 %. Their unfavourable social conditions are demonstrated.

The social status of the entire sample underwent a manifest improvement during the children's first three years of life. The main improvement was in the housing standard. An improvement of real income was also noticeable. While 5.. per cent of the children lived in unsatisfactory housing conditions at birth, the figure was 28 per cent at 3 years of age. As regards mother's occupation only 15 per cent had half time or full time employment from one to three years after the child's birth.

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	1st born		2nd born		3rd born and more		Total
	n	%	n	%	n	%	n
Swedish social group							
I	11	[illegible]	18	51	6	17	35
II	8	35	35	44	16	20	79
III	45	46	37	38	16	[illegible]	98
T tal	84		90		38		1
Graff social class							
I+II	[illegible]0	38	[illegible]5	47	8	16	53
III	27	42	6	41	11	17	64
IV+V	37	39	39	41	19	[illegible]0	95
Total	84		90		38		12

TABLE 22 *Distribution of siblings*

(The twins in three pairs f twins have been gi en the same successional number)

Number f older siblings	Numbe of children n	%	Number of hildren who got a younger sibling[a] bef re 1 yea	between 1 years	between -3 years	up t 3 years of ge
0	84	40	1	18	10	[illegible]
1	90	4	1		7	15
	[illegible]2	10		1		3
3	12	6		1	1	
4		1				
[illegible]		1				
Total	1			[illegible]7	20	49

[a] No child got two younger siblings during the first 3 years.

TABLE 23 *Size of the households*

N mber of persons	Age of children 1 year (n = 12) n	%	2 years (n = [illegible]01) n	%	3 years (n = 206) n	%
	0	0	0	0		1
3	60	33	56	5	49	24
4	88	43	85	42	95	46
5	29	14	38	19	36	18
6	18	9	1[illegible]	7	11	5
7	4	2	5	3	8	4
8 and more	3	1	3	2		1
In hildren home	1	0.5	1	0 5	3	2

TABLE 1. *Health situation in the total material.*

	Health at examination					
		Not healthy				
	Healthy	Prob. of no signif.	Convalescent	Mildly ill	Ill	Total
Health since last visit [a]	724	17	0	3	4	748
[b] Prob. of no signif.	420	111	17	47	2	597
[b] Questionable influence	72	13	20	24	8	137
Signif. influence	8	0	3	3	2	16
Total	1224	141	40	77	16	1498

[a] Healthy. [b] Not healthy.

head circumference were measured at birth. Thereafter the children were examined on eight occasions until the age of 3 years, namely at 1 month (4 weeks), 3 months (13 weeks), 6 months (26 weeks), 9 months (39 weeks), 12 months (52 weeks) and at 18 months, 2 years, and 3 years. Each examination was made on an exact date with a variation of ± 1 day at 1 month, ± 1 week from 3 months to 18 months and $\pm$ weeks from 2 to 3 years.

As from the age of 1 month the examina-

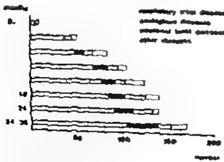

Fig. 1. Number of children with serious illness experiences (including only *the most important* ones) during the intervals between examinations.

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Weight—nude weighing, up to 15 kg with an accuracy of 0.01 kg and thereafter with an accuracy of 0.1 kg.

Length as *recumbent length* and *crown-rump length* measured with the child lying supine on a special table fitted with a measuring tape and sliding footboard, the measurements were made with an accuracy of 0.1 cm.

Femur bicondylar and *humerus bicondylar widths* measured with the knee and the elbow respectively flexed at 90°. *Biacromial* and *pelvic widths* measured between the most lateral points of the acromion and the iliac crest respectively; special metal calipers graded in mm were used.

Head circumference and *chest circumference*, the latter measured at the level of the mamilla at mid-respiration; *upper-arm* and *calf circumferences* recorded as maximum circumferences at passive flexion of the elbow and the knee respectively; a metal tape graded in mm was used.

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Acta Pædiatrica Scandinavica Suppl 187 48–60 1968

The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study

III. Physical Growth during the First Three Years of Life

by PETTER KARLBERG, INGA ENGSTRÖM, HENRIK LICHTENSTEIN and INGA SVENNBERG

A child's physical development is a complex phenomenon which can be fairly well described by means of several body measurements. The more numerous the measurements, the more differentiated will be the picture obtained, even though height and weight alone can often give valuable information.

Knowledge of physical development and its normal variations is a necessary tool in assessing a child's state of health, as the course of an illness and the influence of treatment, among other factors, often affect growth and are reflected by it.

In assessing a single measurement of a child, data from cross-sectional studies of healthy children can be used for comparison. For the purpose of assessing the rate of growth of children by repeated measurements, standards based on cross-sectional data are inadequate. They give only mean values with standard deviations at each age. The means are often connected to form a line which simulates an average individual's development. But this method provides no answer to the question: What are the normal limits of the deviation from the slope of the constructed curve? Such information can be obtained only by longitudinal studies, where repeated measurements of each child are made at regular intervals over a period of time. The longitudinal method yields not only data on distance, that is, the child's size attained at each age, but also on the difference in attained distance between the ages, which is best described as an increment and thus represents the rate of growth.

This paper presents longitudinal data relating to the physical development during the first three years of life of Swedish children in an urban community.

Recruitment took place over the years 1955–1958 and data used in the present study were collected between 1955 and 1960.

For the planning of the study and other details, see Paper I in the series [8].

Material and Methods

The study comprised originally 212 children, 122 boys and 90 girls. By the time the children had reached the age of 3 years, 3 had dropped out because the families had moved abroad. Length, weight and

TABLE 1 *Health situation in the total material*

		Health at examination					
			Not healthy				
		Healthy	Prob. of no signif.	Convalescent	Mildly ill	Ill	Total
Health since last visit		724	*17*	0	3	4	748
	Prob. of no signif.	520	*111*	17	47	2	697
	Questionable influence	73	[illegible]	20	24	8	137
	Signif. influence	8	0	3	3	2	16
	Total	1334	141	40	77	16	1598

Healthy Not healthy

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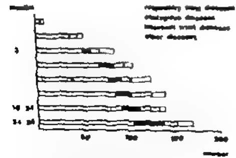

Fig. 1 Number of children with various illness experiences (including only the most important ones) during the intervals between examinations.

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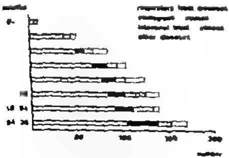

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and its thickness measured with the Harpenden Skinfold Calipers [3] graded in 0.2 mm. The mean of three measurements was used

Anterior fontanel measured as the shortest distance between parallel bone edges with a metal tape graded in mm

For further details see Falkner F., Mod. probl. in ped V 1960 Chapter VI page 70 [4]

At the measuring sessions the children were examined clinically and any illnesses they might have had since the previous visit were recorded From these data the child's present health as well as its health retrospectively between the visits could be assessed With very few exceptions, all the measurements and assessments were made by the same paediatrician (H. L.) throughout.

State of Health of the Sample

In order to use the obtained measurements for analyses of the normal growth pattern it is necessary to assess the state of health of the children in the group

Table 1 shows the examiner's assessment of the present health of the children, that is, at the time of the examination, in relation to health since the last visit It will be seen that the great majority of the children were considered to be in good health at the time of the examination and that about half of them had had some illness during the interval between the visits. Contagious diseases without complications, banal respiratory tract infection occasional diarrhoea minor operations, and accidents were regarded as conditions of probably no significance in the development of the child Diseases, judged as having either a questionable or a significant influence on the child's development occurred relatively sparsely Only 6 children were considered to have been severely ill during the period of investigation.[1]

In Fig 1 is a graphic representation of the diseases judged to have been the most important during the intervals between examinations

Respiratory tract infection was clearly the most common illness and increasingly so as the children grew older

Children who had had no disease throughout the whole period of investigation (the first 3 years of life) must be regarded as extremes. As our material is representative in so many respects (Paper I) it may be assumed that the state of health and the illness experiences found in the group are characteristic of a normal child population. Therefore no child was excluded from the group for reasons of health.

Longitudinality of the Sample

A pure longitudinal sample with each child attending every measuring session would of course be ideal in a longitudinal study But with such strict criteria it would be almost impossible to obtain a non-selected group since such a pure longitudinal sample can be assumed to consist of the very healthy children and/or the most conscientious mothers.

---

[1] *Case* 078, pylorostenosis, age 3 weeks–3 mos, bronchopneumonia age 6 mos,
083 tromboeythopathia diagnosed at age 11 mos;
086, pertussis age 9–11 mos,
1 7 pertussis age 1 14 mos,
146, congenital heart disease (atrial septal defect) operated age 7 yrs;
154 craniosynosthosis diagnosed at age 11 mos, operated at age 1 mos, not in the study since then.

TABLE 2. *Grouping of material by attendance frequency*

	Boys	Girls	Total	%
8 examinations	66	44	110	52
7 examinations	44	26	70	33
longitudinal sample	110	70	180	85
rest sample	12	20	32	15
Total sample	122	90	212	100

Table 2 shows the grouping of the material by attendance frequency. The pure longitudinal sample, that is, children who attended all the eight examinations, comprises 52 %, and the group attending all but one examination 32 % of the material. For augmentation of the longitudinal group

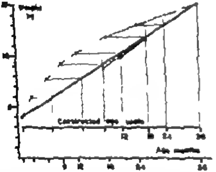

Fig. 2. Graphic interpolation of missing body measurements for given ages taking into consideration the curvilinear relationship to age. The figure shows the procedure used for weight. The curvilinear relationship described by the line connecting the found mean values for each studied age (— —), has been transformed into a rectilinear line by construction of a new age-scale (along the abscissa) in the following way: The plots for the mean weight at 1 and 36 months are connected by a straight line. The obtained mean values of weight for the ages 3, 6, 9, 12, 18 and 24 months are moved horizontally to that line. By vertical lines from these points a new age-scale is constructed. An example is given of interpolation of a missed 12 month value (x—) using the constructed age-scale. Note the graph can only be applied to ages used for its construction.

we considered interpolation of length, weight, and head circumference justifiable in those cases where the children missed one measuring session, excluding those 7 children who failed to attend at 1 month and at 3 years, respectively. Interpolation was made by a graphic method (Fig. 2) on the basis of the mean values derived from the pure longitudinal group.

In 15 % of the sample the children missed two or more examinations, the figures for non-attendance being evenly distributed over the period of examination. This group is referred to as the rest sample. It also includes the 6 ill children. The rest sample was tested against the longitudinal sample: no significant difference was obtained. (Out of 256 analyses only 3 showed significant differences at the 5 % level, which is within the range of variability of the statistical methods.) The two groups were therefore brought together into total sample, which was used for the analyses.

Results

The total sample was used for calculations of means and percentiles. As regards increments, the material is slightly smaller owing to some missed values.

Mean values with S.D. both for distance and for increments were calculated for each body measurement and each age (= exami-

and its thickness measured with the Harpenden Skinfold Calipers [3] graded in 0.2 mm. The mean of three measurements was used

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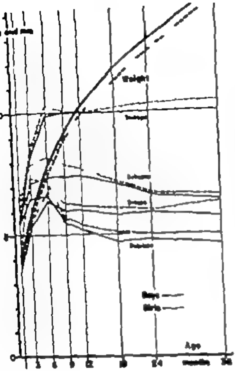


Fig 5

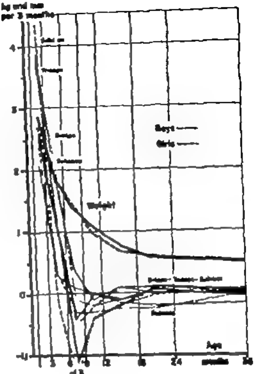


Fig. 6

Fig. 5. Distance attained in weight and skinfolds. Mean values at the various ages connected by lines. Boys and girls separately

Fig. 6. Velocity curves for skinfolds and weight. Mean values of increment in weight and skinfolds between the various ages transformed into units/3 months. Boys and girls separately

nation) for boys and girls separately These values will be seen in Appendix 1 and 2

The percentiles were also calculated (10th, 25th, 50th, 75th and 90th percentiles) both for distance and for increments. These values are set out in Appendix 3 and 4.

The mean values at the different ages for lengths, widths, circumferences, and weight are shown graphically for distance in Fig 3 and for increments in Fig. 4. As regards increments, the values are in the figures not recorded as the difference between the values obtained on the particular occasions, as these represent the changes within a varying period of time, 2, 3, 6 or 12 months, depending upon the fixed intervals between the examinations. For the sake of uniformity and comparison, increments were therefore converted into values representing a 3-month period. T illustrate the relative growth and the relative change in growth velocity the means for distance and increments respectively at the various ages were plotted on a semilogarithmic scale and connected by lines.

Skinfolds as representative of the subcutaneous tissue do not always increase with increasing age, which means that increments can be negative. Therefore, these

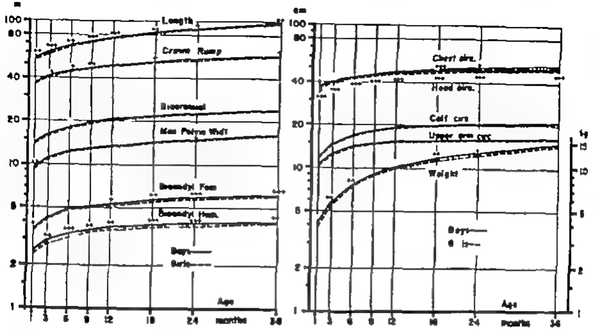


Fig 3 Distance attained in length, widths, circumferences and weight. Mean values at the various ages connected by lines. Boys and girls separately Significance of sex difference marked $p < 0.05$, $p < 0.01$ $p < 0.001$

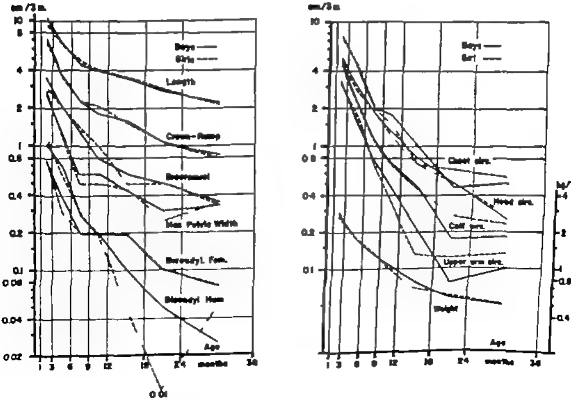
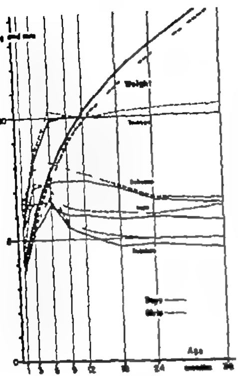


Fig 4 Velocity curves for the different measurements. Mean values of increment in body measurements between the various ages transformed into units/3 months. Boys and girls separately



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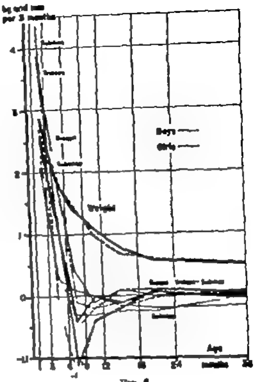

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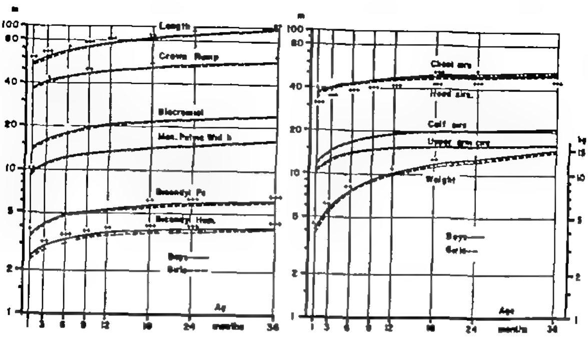

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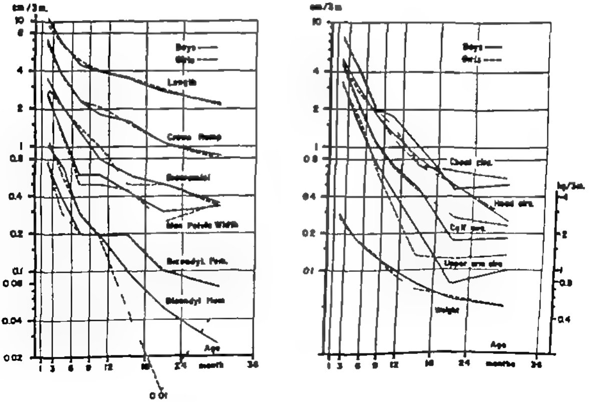

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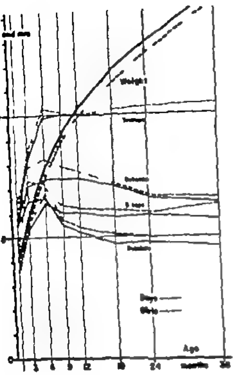

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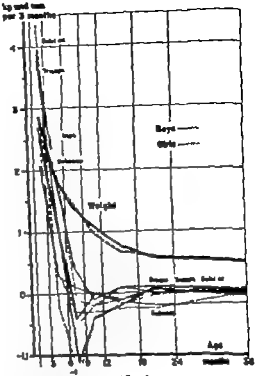

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TABLE 3 *Sex differences in the various body measurements at each age.*

	1	3	6	9	12	18	24	36
Weight								
Length					*			
Crown-rump length								
Chest circumf								
Head circumf.					*			
Upper arm circumf.								
Calf circumf.								
Bicondyl femur							*	
Bicondyl. humerus			*		*			
Max. pelvic width								
Biacromial width								
Subcut. biceps								**
triceps								
subscap.								**
suprailiac.								**

$p < 0.05$ $p < 0.01$ * $p < 0.001$ boys > girls.
$p < 0.05$, ** $p < 0.01$ *** $p < 0.001$ girls > boys.

values cannot be rendered logarithmically So for the sake of uniformity both distance and increments for skinfolds are shown on a metric scale in Figs 5 and 6 For comparison, the weight is also shown

A numerical sex difference with preponderance for boys is noted in all the measurements, excluding those of skinfolds, where there is a preponderance for the girls. The found sex differences are significant in most of the cases (Table 3)

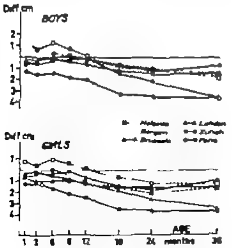


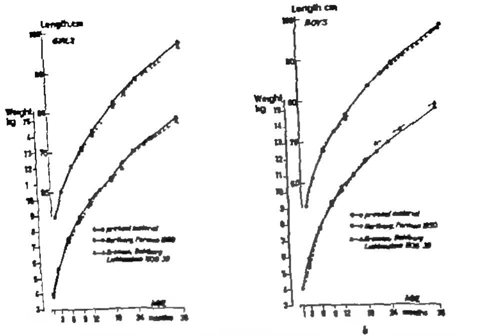
Fig 7 Deviation from present study in mean length at the various ages in studies from London [13], Paris [9], Brussels [5], Zürich [6], Helsinki [1] and Bergen [10].

Discussion

It is evident that growth, in general, for all the variables, particularly in the first half year of life occurs at a high but gradually decreasing rate The relative growth in length and in widths is on the whole similar The growth in total length is more rapid, however than the crown-rump growth which illustrates the well known fact that the legs grow quicker than the trunk.

Head circumference and chest circumference are evidently similar for each age during the whole period. But a tendency to more rapid growth in chest circumference during the second year of life is noted.

The relative gain occurs faster in weight than in length widths, and circumferences, in accordance with the fact that weight is three-dimensional whereas the others are one-dimensional.



Figs. 8a and 8b Graphical comparison of mean length obtained in present and previous Swedish studies [2, 7].

The difference in length between boys and girls seems to be due mainly to greater total length and less to greater crown-rump length in boys. As femur and humerus bicondylar widths are also significantly greater in boys than in girls, it seems that particularly the extremities are bigger in the boys. Another striking observation is that the head is constantly bigger in boys than in girls throughout the series.

As regards weight, the values are also higher for boys than for girls, but the difference is not so highly significant as for the bony width measurements. The only body measurement that shows a numerical difference in favour of the girls is that of skinfolds, indicating a greater amount of subcutaneous fat in girls. This difference, however is significant only at the age of 3 years. The poor significance may imply that the random error of the method is greater because of the difficulties in standardizing the technique of measuring.

The fact that the girls have more subcutaneous fat than the boys may account for the small difference in weight between the sexes, in spite of greater length and bony widths in the boys. The small differences in arm, calf, and chest circumferences as well as in pelvic and biacromial widths between the sexes could also be explained by the greater amount of subcutaneous fat in the girls included in these measurements.

The basic difference between boys and girls up to age 3 thus seems to be a predominance of skeletal tissue in boys and of subcutaneous tissue in girls.

A comparison between our values for length and the values obtained in the coordinated longitudinal studies from London [13] Paris [9], Brussels [5], and Zürich [6]

TABLE 3 *Sex differences in the various body measurements at each age*

	1	3	6	9	1	[illegible]	4	36
Weight								
Length								
Crown-rump length								
Chest circumf								
Head circumf								
Upper arm circumf								
Calf circumf								
Bicondyl. femur								
Bicondyl. humerus								
Max. pelvic width								
Biacromial width								
Subcut. biceps								**
triceps								
subscap.								**
subiliac.								**

$p<0.05$, $p<0.01$ $p<0.001$ boys > girls.
$p<0.05$ $^{**}p<0.01$ $^{***}p<0.001$ girls > boys.

values cannot be rendered logarithmically So for the sake of uniformity both distance and increments for skinfolds are shown on a metric scale in Figs. 5 and 6 For comparison the weight is also shown

A numerical sex difference with preponderance for boys is noted in all the measurements, excluding those of skinfolds, where there is a preponderance for the girls. The found sex differences are significant in most of the cases (Table 3)

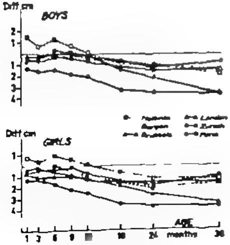


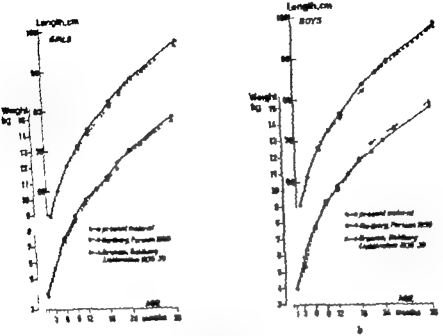
Fig 7 Deviation from present study in mean length at the various ages in studies from London [13], Paris [9], Brussels [5], Zurich [6], Helsinki [1] and Bergen [10].

Discussion

It is evident that growth, in general for all the variables, particularly in the first half year of life occurs at a high but gradually decreasing rate The relative growth in length and in widths is on the whole similar The growth in total length is more rapid, however than the crown-rump growth, which illustrates the well known fact that the legs grow quicker than the trunk.

Head circumference and chest circumference are evidently similar for each age during the whole period But a tendency to more rapid growth in chest circumference during the second year of life is noted

The relative gain occurs faster in weight than in length widths, and circumferences, in accordance with the fact that weight is three-dimensional whereas the others are one-dimensional



Figs 8 and 8b. Graphical comparison of mean length obtained in present and previous Swedish studies (2, 7).

The difference in length between boys and girls seems to be due mainly to greater total length and less to greater crown-rump length in boys. As femur and humerus bicondylar widths are also significantly greater in boys than in girls, it seems that particularly the extremities are bigger in the boys. Another striking observation is that the head is constantly bigger in boys than in girls throughout the series.

As regard weight, the values are also higher for boys than for girls, but the difference is not so highly significant as for the bony width measurements. The only body measurement that shows a numerical difference in favour of the girls is that of skinfolds, indicating a greater amount of subcutaneous fat in girls. This difference however is significant only at the age of 3 years. The poor significance may imply that the random error of the method is greater because of the difficulties in standardizing the technique of measuring.

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The basic difference between boys and girls up to age 3 thus seems to be a predominance of skeletal tissue in boys and of subcutaneous tissue in girls.

A comparison between our values for length and the values obtained in the coordinated longitudinal studies from London [13], Paris [9], Brussels [5], and Zürich [6]

TABLE 3 *Sex differences in the various body measurements at each age*

	1	3	6	9	1	18	4	36
Weight								
Length								
Crown-rump length								
Chest circumf.								
Head circumf								
Upper arm circumf.								
Calf circumf								
Bicondyl. femur								
Bicondyl. humerus								
Max. pelvic width								
Biacromial width								
Subcut. biceps								**
triceps								
subscap.								**
subiliac.								**

$p < 0.05$ $p < 0.01$ $p < 0.001$ boys > girls.
$^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$ girls > boys.

values cannot be rendered logarithmically So for the sake of uniformity both distance and increments for skinfolds are shown on a metric scale in Figs. 5 and 6 For comparison the weight is also shown.

A numerical sex difference with preponderance for boys is noted in all the measurements, excluding those of skinfolds, where there is a preponderance for the girls. The found sex differences are significant in most of the cases (Table 3)

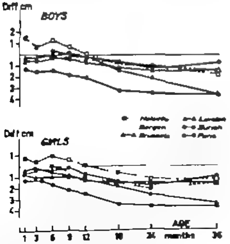


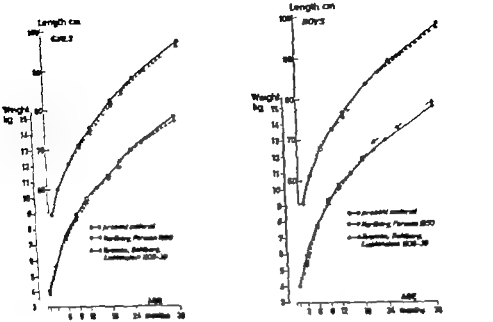
Fig 7 Deviation from present study in mean length at the various ages in studies from London [13], Paris [9], Brussels [5], Zürich [6], Helsinki [1] and Bergen [10].

Discussion

It is evident that growth in general, for all the variables, particularly in the first half year of life occurs at a high but gradually decreasing rate The relative growth in length and in widths is on the whole similar The growth in total length is more rapid, however than the crown-rump growth, which illustrates the well known fact that the legs grow quicker than the trunk.

Head circumference and chest circumference are evidently similar for each age during the whole period. But a tendency to more rapid growth in chest circumference during the second year of life is noted

The relative gain occurs faster in weight than in length, widths, and circumferences, in accordance with the fact that weight is three-dimensional whereas the others are one-dimensional.



b

Figs. 5a and 5b. Graphical comparison of mean length obtained in present and previous Swedish studies [2, 7].

The difference in length between boys and girls seems to be due mainly to greater total length and less to greater crown-rump length in boys. As femur and humerus bicondylar widths are also significantly greater in boys than in girls it seems that particularly the extremities are bigger in the boys. Another striking observation is that the head is constantly bigger in boys than in girls throughout the series.

As regards weight, the values are also higher for boys than for girls, but the difference is not so highly significant as for the bony width measurements. The only body measurement that shows a numerical difference in favour of the girls is that of skinfolds, indicating a greater amount of subcutaneous fat in girls. This difference however is significant only at the age of 3 years. The poor significance may imply that the random error of the method is greater because of the difficulties in standardizing the technique of measuring.

The fact that the girls have more subcutaneous fat than the boys may account for the small difference in weight between the sexes, in spite of greater length and bony widths in the boys. The small differences in arm, calf, and chest circumferences as well as in pelvic and biacromial widths between the sexes could also be explained by the greater amount of subcutaneous fat in the girls included in these measurements.

The basic difference between boys and girls up to age 3 thus seems to be a predominance of skeletal tissue in boys and of subcutaneous tissue in girls.

A comparison between our values for length and the values obtained in the coordinated longitudinal studies from London [13], Paris [9], Brussels [5], and Zürich [6]

TABLE 3 *Sex differences in the various body measurements at each age*

	1	3	6	9	12	18	4	36
W ight								
Length								
Crown–rump length								
Chest circumf								
Head circumf								
Upper arm circumf								
Calf circumf								
Bicondyl. femur								
Bicondyl. humerus						*		
Max. pelvic width								
Biacromial width								
Subcut. biceps								**
triceps								
subscap								**
subiliac.								**

$p<0\ 05$ $p<0\ 01$ $p<0\ 001$ boys > girls.
$p<0\ 05$, $^{**}p<0\ 01$ $^{***}p<0\ 001$ girls > boys.

values cannot be rendered logarithmically So for the sake of uniformity both distance and increments for skinfolds are shown on a *metric scale in Figs 5 and 6 For com*parison, the weight is also shown.

A numerical sex difference with preponderance for boys is noted in all the measurements, excluding those of skinfolds, where there is a preponderance for the girls. The found sex differences are significant in most of the cases (Table 3)

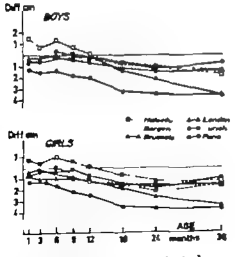


Fig 7 Deviation from present study in mean length at the various ages in studies from London [13], Paris [9], Brussels [5], Zürich [6], Helsinki [1] and Bergen [10].

Discussion

It is evident that growth in general for all the variables, particularly in the first half year of life occurs at a high but gradually decreasing rate. The relative growth in length and in widths is on the whole similar The growth in total length is more rapid, however than the crown-rump growth, which illustrates the well known fact that the legs grow quicker than the trunk.

Head circumference and chest circumference are evidently similar for each age during the whole period *But a tendency* to more rapid growth in chest circumference during the second year of life is noted.

The relative gain occurs *faster* in weight than in length widths, and circumferences, in accordance with the fact that weight is three-dimensional whereas the others are one-dimensional

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APPENDIX 1 *Mean values with s.d for distance attained at each age for each body measurement in girls and boys separately*

Age in mos	Sex	No.	Weight in kg Mean	s.d.	Length in cm Mean	s.d	Crown-rump in cm Mean	s.d.	Head circumf. in cm Mean	s.d.	Chest circumf. in cm Mean	s.d
0	G	83	3 48	0.39	50.2	1.8			33.0	1.2		
	B	121	3 67	0.46	51.0	2.3			33.4	1.3		
1	G	85	3.83	0.41	53.7	2.0	36.0	1.5	36.2	1 0	34.2	1 4
	B	114	4.00	0.55	54.6	2.1	36 5	1.5	37.0	1.2	34 7	1.9
3	G	87	5 80	0.50	60.0	2.0	40.4	1.6	39.2	1.0	38.9	1.8
	B	120	5.90	0.61	61.3	2.3	41.1	1.8	40.1	1.1	39.3	2.1
6	G	86	7 47	0.73	66.6	2 3	44.2	1.7	42.1	1.0	43.3	2.0
	B	120	7 77	0.81	67.9	2.0	44.6	1.6	43.3	1.2	43.8	2.5
9	G	86	8.49	0 78	71.2	2.2	46.4	1.7	44.0	1.0	45.3	1.8
	B	121	9 13	1.05	72.6	2.1	47 1	1.6	45 2	1.2	45.7	2.3
12	G	87	9 80	0.87	75.3	2.4	48.6	1.7	45.3	1.0	46.9	2.1
	B	121	10.23	1 12	76.6	2.3	49.0	1 7	46.5	1 1	47 4	2.3
18	G	86	11..3	0 96	82.3	2.8	51.6	1 7	46.6	1.0	48.2	2.3
	B	118	11 78	1.22	83.5	2.7	52.2	1.8	48.0	1.3	49.3	2.4
24	G	81	1..43	1.21	87 9	2.1	53.7	2.1	47.6	1.4	49 6	2.3
	B	120	12.93	1.43	89 0	2.0	54.2	2.1	49 0	1.3	50 3	2.5
36	G	82	14.56	1.57	96.3	3 0	57.0	2.1	48.7	1.1	51.6	2.3
	B	114	14.94	1.83	97.4	3.7	57 7	2.4	50.0	1.3	52 4	[illegible]

(Fig 7) shows that the Swedish children agree best with the Zürich children and least with the Paris children. The latter are in general 1–4 cm shorter than the Swedish children

In the graphs are also plotted the difference between the Swedish values and the ones obtained in cross-sectional studies from Bergen [10] and Helsinki [1]. The Helsinki children are taller than the Swedish children during the first year of life but tend to be somewhat shorter later on. The Bergen children are from one year of life 1–2 cm shorter than the Swedish children. It must be taken into consideration however that at age 3 the Bergen children were measured in the standing position, which gives lower figures than do measurements in the recumbent position [12]

The means for length and weight are graphically compared (Figs. 8*a* and *b*) with earlier Swedish values [7 2] The values in the present study are in close agreement with those obtained by Karlberg & Perman [7] in the years 1950–52, which form the standards used in Sweden for children up to 1½ years. These values, in turn are very close to those found in a previous Swedish study of weight during the first 12 months of life in children with a birth weight of 3 0–3.5 kg [11] Earlier Swedish investigations of length in this age group are not available for comparison. Swedish standards for the ages above 1½ years are based upon the study published by Broman Dahlberg & Lichtenstein in 194? [2] sampled in 1938–39 These values are thus 20 years older than those obtained in this study In this period of time it would be reasonable to expect a secular trend The slight difference between the children in the present and in the earlier study however is difficult to evaluate as the older values are based upon only a few measurements in each group (around 35) with a wide age range (6 months)

Summary

The physical growth was followed longitudinally from birth to 3 years of age in a group of 212 randomly sampled children from the Stockholm urban area 122 boys and 90 girls. The children were measured on eight occasions at fixed intervals.

Recumbent length crown–rump length weight femur bicondylar and humerus bicondylar width biacromial and pelvic width, circumference of head and chest, subcutaneous tissue at four different sites and the anterior fontanel were measured.

The mean values for these measurements with S.D as well as the percentiles are given The increments were calculated and are also given as means with S.D and percentiles.

The pattern of growth is discussed. Differences between boys and girls were found, particularly with respect to the skeletal and the subcutaneous tissue the former being more developed in boys and the latter in girls.

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Appendix 1 *Mean values with S.D. for distance attained at each age for each body measurement in girls and boys separately*

Age in mos	Sex	No.	Weight in kg Mean	S.D.	Length in cm Mean	S.D.	Crown-rump in cm Mean	S.D.	Head circumf. in cm Mean	S.D.	Chest circumf. in cm Mean	S.D.
0	G	88	3.45	0.39	50.2	1.8			34.0	1.2		
	B	131	3.57	0.55	51.0	2.2			34.4	1.5		
1	G	85	3.88	0.41	53.7	2.0	36.0	1.5	36.2	1.0	34.3	1.4
	B	114	4.03	0.55	54.5	2.1	36.6	1.5	37.0	1.3	34.7	1.9
3	G	87	5.59	0.50	60.0	2.0	40.4	1.5	39.3	1.0	38.9	1.8
	B	130	5.90	0.81	61.3	2.2	41.1	1.6	40.1	1.1	39.3	2.1
6	G	88	7.47	0.72	65.6	2.3	44.3	1.7	42.1	1.0	42.3	2.0
	B	120	7.77	0.91	67.0	2.0	44.5	1.6	43.3	1.3	42.6	2.5
9	G	88	8.59	0.75	71.2	2.3	46.4	1.7	44.0	1.0	43.2	1.6
	B	131	9.13	1.05	72.5	2.1	47.1	1.8	45.2	1.5	45.7	2.2
12	G	87	9.50	0.87	73.3	2.4	48.5	1.7	45.3	1.0	46.9	2.1
	B	121	10.23	1.12	76.8	2.3	49.0	1.7	46.6	1.1	47.4	2.3
18	G	86	11.33	0.95	82.3	2.8	51.6	1.7	46.6	1.0	48.2	2.3
	B	118	11.78	1.32	83.5	2.7	52.2	1.9	48.0	1.3	48.3	2.4
24	G	84	12.43	1.21	87.8	3.1	53.7	2.1	47.8	1.4	49.6	2.3
	B	120	12.94	1.33	89.0	3.0	54.2	2.1	49.0	1.3	50.2	2.5
36	G	82	14.64	1.57	94.5	2.6	57.0	2.1	48.7	1.1	51.6	2.3
	B	114	14.93	1.39	97.5	2.7	57.7	2.4	50.0	1.3	52.4	2.6

Appendix 1 (*cont*)

Age in mos	Sex	No	Upper arm circumf. in cm Mean	s.D	Calf circumf in cm Mean	s.D	Bicondyl. femur in cm Mean	s.D	Bicondyl. humerus in cm Mean	s.D	Max. pelvic width in cm Mean	s.D	Biacromial in cm Mean	s.D.
1	G	85	10.4	0.7	12.0	0.6	3.4	0.2	2.4	0.2	9.0	0.8	13.6	0.6
	B	114	10.4	1.0	12.0	1.0	3.5	0.3	2.4	0.4	9.4	[illegible]	14.0	1.0
3	G	84	12.4	1.1	15.0	1.0	4.2	0.4	2.8	0.3	11.0	0.9	15.9	1.0
	B	114	12.5	1.3	15.0	1.4	4.2	0.4	3.0	0.4	11.1	0.8	16.2	1.1
6	G	85	14.2	1.1	17.3	1.1	4.7	0.4	3.2	0.3	12.3	1.3	17.9	1.3
	B	113	14.2	1.1	17.3	1.4	4.8	0.4	3.3	0.3	12.3	0.8	18.2	1.1
9	G	83	15.0	1.0	18.4	1.1	5.0	0.3	3.4	0.2	12.8	0.8	19.3	1.0
	B	119	15.0	1.1	18.3	1.3	5.1	0.4	3.5	0.3	12.9	0.9	19.6	1.0
12	G	84	15.4	1.0	19.1	1.2	5.2	0.3	3.6	0.2	13.3	0.8	20.4	1.1
	B	121	15.5	1.3	19.1	1.3	5.3	0.4	3.7	0.2	13.4	0.8	20.4	1.0
18	[illegible]	81	15.6	1.1	20.0	1.3	5.5	0.4	3.7	0.3	14.1	1.1	21.3	1.3
	B	113	15.9	1.2	20.1	1.3	5.7	0.4	3.8	0.3	14.4	0.8	21.6	1.1
24	[illegible]	83	15.9	1.1	20.5	1.3	5.7	0.3	3.7	0.2	14.7	0.7	22.4	1.3
	B	117	16.0	1.2	20.5	1.4	5.9	0.4	3.9	0.3	15.0	0.8	22.5	1.1
36	G	83	16.4	1.0	21.4	1.3	6.0	0.3	3.9	0.2	16.0	0.7	23.9	1.2
	B	119	16.5	1.2	21.2	1.3	6.2	0.4	4.0	0.2	16.3	1.2	24.0	1.3

Age in mos	Sex	No	Skinfold measurements: Biceps in mm Mean	s.D	Triceps in mm Mean	s.D	Subscap. in mm Mean	s.D	Subiliac. in mm Mean	s.D	Ant. Fontanel in cm Mean	s.D
1	G	84	[illegible]	0.6	5.9	1.2	6.4	1.3	4.4	1.0	2.6	[illegible]
	B	114	3.6	0.7	5.5	1.3	5.7	1.2	4.1	1.1	2.9	0.9
3	G	84	5.6	1.2	8.4	1.7	7.8	1.6	7.2	1.9	2.5	0.8
	B	114	5.3	1.2	8.1	1.8	7.1	1.8	6.5	2.1	2.4	0.9
6	[illegible]	85	6.8	1.7	10.2	1.8	8.2	2.1	7.2	2.3	2.2	0.9
	B	113	6.4	1.6	9.9	1.8	7.4	1.6	6.6	2.3	2.1	0.9
9	[illegible]	83	6.3	1.1	10.1	1.7	7.9	1.6	5.7	1.5	1.7	[illegible]
	B	119	6.0	1.3	10.0	2.0	7.4	2.0	5.5	1.5	1.6	1.3
12	G	82	6.2	1.2	10.0	1.6	7.7	1.6	5.4	1.2	1.1	1.0
	B	120	6.0	1.3	10.0	1.9	7.4	1.8	5.2	1.5	1.1	0.9
18	G	74	6.1	1.2	10.2	1.7	7.2	1.5	5.1	1.2	0.2	0.6
	B	110	5.8	1.1	10.0	1.8	7.1	1.6	4.7	1.1	0.3	0.6
24	G	78	6.0	1.2	10.3	1.9	6.7	1.4	5.0	1.2	0.1	0.2
	B	112	5.9	1.2	10.0	2.1	6.6	1.6	4.8	1.7	0.0	0.2
36	G	80	6.3	1.6	10.4	2.0	6.6	2.0	5.0	1.2	—	—
	B	114	5.7	1.1	10.0	1.7	5.9	1.5	4.6	1.2	—	—

APPENDIX 2 *Mean values with S.D for increment between each age for each body measurement in girls and boys separately*

Age in mos	Sex	No.	Weight in kg Mean	Weight in kg S.D	Length in cm Mean	Length in cm S.D	Crown-rump in cm Mean	Crown-rump in cm S.D	Head circumf. in cm Mean	Head circumf. in cm S.D	Chest circumf. in cm Mean	Chest circumf. in cm S.D
0–1	G	82	0.42	0.26	3.6	1.4	—	—	[illegible]	1.2	—	—
	B	114	0.43	0.20	3.5	1.3	—	—	3.6	1.3	—	—
1–3	G	81	1.76	0.30	6.2	1.4	4.4	1.1	3.1	0.6	4.7	1.5
	B	105	1.91	0.52	7.0	1.3	4.7	1.4	3.3	0.7	4.8	1.8
3–6	G	76	1.57	0.51	6.5	1.4	2.7	1.3	2.6	0.5	4.6	1.9
	B	104	1.60	0.64	6.6	1.6	2.8	1.3	3.1	0.7	4.4	2.1
6–9	G	78	1.44	0.51	4.8	1.2	2.5	1.6	1.9	0.5	2.0	1.8
	B	106	1.37	0.44	4.5	1.3	2.3	1.4	1.9	0.4	2.0	1.6
9–12	G	86	1.09	0.36	4.1	1.0	2.1	1.3	1.2	0.4	1.5	1.5
	B	121	1.10	0.56	4.0	1.0	1.8	1.3	1.3	0.4	1.8	1.7
12–18	G	74	1.29	0.50	7.3	1.3	2.1	1.1	1.4	0.5	1.4	1.3
	B	107	1.56	0.56	7.1	1.5	2.2	1.1	1.6	0.5	2.0	1.6
18–24	G	75	1.19	0.50	5.7	1.2	2.1	1.5	1.0	0.5	1.3	1.6
	B	106	1.12	0.58	5.5	1.2	2.1	1.2	1.0	0.6	0.9	1.6
24–36	G	77	2.10	0.60	8.5	1.2	2.2	1.0	1.1	0.5	[illegible]	1.6
	B	114	1.98	0.66	8.7	1.5	2.4	1.2	1.0	0.5	2.0	1.6

Age in mos	Sex	N	Upper arm circumf. in cm Mean	Upper arm circumf. in cm S.D	Calf circumf. in cm Mean	Calf circumf. in cm S.D.	Biepicondyl. femur in cm Mean	Biepicondyl. femur in cm S.D	Biepicondyl. humerus in cm Mean	Biepicondyl. humerus in cm S.D	Max. pelvis width in cm Mean	Max. pelvis width in cm S.D	Biacromial in cm Mean	Biacromial in cm S.D.
1–3	G	81	2.1	1.0	3.0	0.8	0.8	0.3	0.6	0.3	1.0	1.1	2.0	0.8
	B	105	2.2	1.1	3.1	1.0	0.7	0.3	0.6	0.5	1.4	0.8	2.3	1.1
3–6	G	78	1.6	1.0	2.4	0.8	0.6	0.3	0.3	0.3	1.2	1.2	2.1	1.2
	B	104	1.7	1.0	2.4	1.0	0.7	0.3	0.4	0.4	1.2	0.7	2.1	1.0
6–9	G	78	0.8	0.9	1.1	0.9	0.2	0.4	0.2	0.3	0.5	1.2	1.4	1.4
	B	106	0.8	0.8	1.1	0.8	0.2	0.2	0.3	0.3	0.6	0.6	1.3	0.9
9–12	G	76	0.6	0.7	0.7	0.9	0.2	0.3	0.2	0.3	0.6	0.6	1.0	0.8
	B	119	0.8	0.9	0.8	0.8	0.2	0.3	0.2	0.3	0.5	0.6	0.8	1.0
12–18	G	72	0.3	0.9	0.9	0.8	0.4	0.2	0.1	0.3	0.9	0.9	1.0	1.2
	B	108	0.4	[illegible]	1.0	0.9	0.4	0.3	0.2	0.2	1.0	0.7	1.2	1.1
18–24	G	71	0.2	0.7	0.6	0.6	0.2	0.2	0.0	0.2	[illegible]	1.0	1.0	1.2
	B	106	0.2	0.7	0.4	0.7	0.2	0.2	0.1	0.2	0.4	0.8	1.0	1.1
24–36	G	77	0.8	0.7	[illegible]	0.8	0.2	0.3	0.2	0.2	1.4	0.5	1.2	0.3
	B	111	0.4	0.9	0.7	0.7	[illegible]	0.3	0.1	0.2	1.3	0.9	1.4	1.2

Appendix (cont.)

Age in mos	Sex	No	Skinfold measurements							
			Biceps in mm		Triceps in mm		Subscap. in mm		Subiliac. in mm	
			Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
1–3	G	81	1 8	1 1	–5	1 7	1 6	1.5	–9	1 9
	B	105	1 7	1 0	6	1 6	1 4	1 6	–5	1 7
3–6	G	78	1 3	1 6	–1	1 9	0.3	1.3	−0.–	–1
	B	101	1.–	1 5	1 9	1	0.3	1 8	1.3	–
6–9	G	78	−0 5	1.5	−0 1	1 7	−0 3	1.5	−1.3	1 9
	B	106	−0 4	1 1	0 4	1 7	0.1	1.5	−1 1	–0
9–1	G	76	−0.–	0.8	−0	1 7	−0.3	1 1	−0.4	1 4
	B	118	−0 0*	1 0	−0 1	1 8	−0.01	1 6	−0 4	1 6
12 18	G	72	−0.3	0.8	0 3	1 6	−0.5	1 3	−0 4	1 1
	B	108	−0	0 9	0.–	1 7	−0.3	1.5	−0.4	1.3
18–24	G	66	0 0	0 9	0.3	1 6	−0.5	1 1	−0.03	1 4
	B	98	0 1	0 7	0 0	1 7	−0 4	1 4	0.–	1 7
4–36	G	72	0.3	1.5	0.0	–1	−0.1	1 7	0.1	1 4
	B	108	−0	1 0	−0 1	1 7	−0 7	1 1	−0.2	1 7

APPENDIX 2. *Percentiles for distance attained at each age for each body measurement in girls and boys separately*

Age in mos	Sex	No.	Percentiles 10	25	50	75	90
Weight in kg							
1	G	85	3.34	3.61	3.85	4.10	4.41
	B	114	3.31	3.60	4.01	4.30	4.68
3	G	[illegible]	4.88	5.20	5.60	5.90	6.18
	B	120	4.88	5.34	5.63	6.37	6.66
6	G	86	6.74	7.00	7.46	7.95	8.37
	B	120	6.71	7.06	7.72	8.20	8.96
9	G	88	7.94	8.25	8.90	9.42	9.67
	B	120	7.91	8.33	9.07	9.65	10.00
12	G	87	8.69	9.18	9.85	10.40	11.11
	B	121	8.84	9.41	10.16	10.85	11.65
18	G	84	10.16	10.94	11.10	11.84	12.70
	B	118	10.19	10.89	11.61	12.55	13.20
24	G	86	11.00	11.50	12.30	13.14	14.16
	B	120	10.90	11.39	12.33	12.95	14.46
36	G	83	12.90	13.42	14.33	15.30	17.00
	B	120	12.80	13.04	14.90	15.70	16.80
Length in cm							
1	G	85	51.3	52.3	53.8	55.2	56.2
	B	114	52.5	53.1	54.8	56.0	57.1
3	G	87	57.5	58.4	60.0	61.3	62.6
	B	120	58.7	60.7	61.8	63.8	64.0
6	G	88	63.5	65.3	66.3	67.8	69.2
	B	120	64.6	66.3	67.8	69.2	70.6
9	G	88	68.5	69.8	71.1	73.1	74.0
	B	121	70.0	70.9	72.3	73.6	75.0
12	G	87	72.6	73.2	75.1	76.9	78.1
	B	121	73.6	74.7	76.4	78.0	79.3
18	G	86	78.7	80.3	82.0	84.2	86.2
	B	118	80.0	81.7	83.3	85.2	87.0
24	G	84	84.3	85.8	87.8	90.3	91.9
	B	120	85.0	87.2	88.8	90.9	92.8
36	G	83	92.1	94.3	96.2	99.0	100.6
	B	114	93.4	95.3	97.3	100.6	102.0
Crown-rump length cm							
1	G	85	34.0	35.0	36.8	37.0	37.7
	B	114	34.3	35.2	36.6	37.6	39.5
3	G	87	38.5	39.3	40.3	41.4	42.3
	B	120	38.1	40.2	41.0	42.0	43.1
6	G	86	41.8	43.1	44.0	[illegible]	46.0
	B	120	43.1	43.8	44.7	45.6	46.6
9	G	88	44.8	45.3	46.3	47.3	48.5
	B	121	45.2	46.3	47.1	48.1	49.3
12	G	87	46.4	47.4	48.5	49.6	50.2
	B	121	46.9	47.7	49.0	50.1	51.0
18	G	85	49.4	50.5	51.9	52.0	53.6
	B	118	49.7	51.1	51.9	53.5	54.4
24	G	84	50.9	52.1	53.8	54.9	56.7
	B	119	51.3	53.0	54.3	55.5	57.0
36	G	80	54.6	55.2	56.8	58.8	60.5
	B	112	54.7	56.0	57.7	59.2	60.9
Head circumf in cm							
1	G	85	35.0	35.6	36.2	36.7	37.6
	B	114	35.2	36.2	37.0	37.8	38.6
3	G	87	37.9	38.7	39.5	39.8	40.4
	B	120	38.6	39.8	40.3	41.0	41.7
6	G	88	40.9	41.5	42.2	42.8	43.4
	B	120	41.3	42.7	43.3	44.0	44.8
9	G	88	42.7	43.3	44.0	44.8	45.5
	B	121	43.7	44.6	45.0	45.6	46.6
12	G	87	44.0	44.8	45.3	45.9	46.6
	B	121	45.0	45.8	46.6	47.2	47.7
18	G	85	45.4	45.9	46.7	47.3	48.2
	B	118	46.4	47.1	48.1	49.0	49.6
24	G	86	46.4	46.8	47.8	48.3	49.0
	B	120	47.3	48.1	49.6	49.7	50.6
36	G	83	47.1	47.8	48.8	49.5	50.1
	B	120	48.0	49.3	50.0	50.9	51.7
Chest circumf in cm							
1	G	86	32.3	33.2	34.2	35.0	35.8
	B	114	32.4	33.4	34.6	35.2	37.0
3	G	87	36.4	37.5	38.8	40.0	41.3
	B	120	36.6	38.0	39.0	40.7	42.1
6	G	86	40.4	42.0	43.3	44.5	45.6
	B	120	40.7	42.0	43.3	45.0	46.7
9	G	88	42.8	44.0	45.3	46.6	47.7
	B	121	42.9	44.3	45.7	46.7	48.5
12	G	87	43.9	45.5	47.0	48.6	49.7
	B	121	44.7	46.0	47.4	49.0	50.3
18	G	85	45.5	46.6	47.8	49.8	51.3
	B	118	46.2	47.7	49.2	50.8	52.8
24	G	81	46.8	47.9	49.2	50.8	52.5
	B	120	47.0	48.8	50.2	51.9	53.3
36	G	81	48.9	50.3	51.2	52.3	54.0
	B	119	49.0	50.7	52.3	53.7	55.0
Upper arm circumf in cm							
1	G	85	9.5	9.9	10.3	10.8	11.3
	B	114	9.4	9.7	10.3	11.0	11.6
3	G	84	11.0	11.7	12.5	13.1	13.5
	B	114	11.0	11.7	12.3	13.5	14.2
6	G	[illegible]	12.7	13.3	14.1	15.0	15.6
	B	113	12.8	13.3	14.1	15.2	15.8
9	G	83	13.7	14.3	14.7	15.6	16.6
	B	119	13.7	14.3	14.9	15.7	16.5

Appendix (*cont.*)

Age in mos	Sex	No	Skinfold measurements: Biceps in mm Mean	S.D	Triceps in mm Mean	S.D	Subscap in mm Mean	S.D	Subiliac in mm Mean	S.D
1–3	G	81	1.8	1.1	2.5	1.7	1.6	1.5	[illegible].9	1.9
	B	105	1.7	1.0	[illegible].6	1.6	1.4	1.6	[illegible].5	1[illegible]
3–6	G	78	1.3	1.6	[illegible].1	1.9	0.3	1.3	−0.[illegible]	[illegible].1
	B	104	1.2	1.5	1.9	1.7	0.3	1.8	1.3	[illegible].2
6–9	G	78	−0.5	1.5	−0.1	1.7	−0.3	1.5	−1.3	1.9
	B	106	−0.4	1.1	0.4	1.7	0.1	1.5	−1.1	[illegible].0
9–12	G	76	−0.[illegible]	0.8	−0.3	1.7	−0.3	1.1	−0.4	1.4
	B	118	−0.0[illegible]	1.0	−0.1	1.8	−0.01	1.6	−0.4	1.6
12–18	G	72	−0.2	0.8	0.[illegible]	1.6	−0.5	1.3	−0.4	1.1
	B	108	−0.2	0.9	0.2	1.7	−0.3	1.5	−0.4	1.3
18–[illegible]4	G	66	0.0	0.9	0.[illegible]	1.6	−0.5	1.1	−0.03	1.4
	B	98	0.1	0.7	0.0	1.7	−0.4	1.4	0.[illegible]	1[illegible]
24–36	G	72	0.3	1.5	0.0	2.1	−0.1	1.7	0.1	1.4
	B	108	−0.2	1.0	−0.1	1.7	−0[illegible]	1.1	−0.[illegible]	1.7

Appendix 3. *Percentiles for distance attained at each age for each body measurement in girls and boys separately*

Age in mos	Sex	No.	10	25	50	75	90
Weight in kg							
1	G	85	3.34	3.61	3.86	4.10	4.41
	B	114	3.31	3.60	4.01	4.30	4.68
3	G	87	4.88	5.20	5.60	5.89	6.18
	B	120	4.88	5.36	5.83	6.27	6.86
6	G	88	6 [illegible]	7.09	7.46	7.85	8.37
	B	120	6.71	7.09	7.72	8.20	8.96
9	G	88	7.94	8.35	8.90	9.43	9.67
	B	120	7.91	8.33	9.07	9.65	10.69
12	G	87	8.90	9.16	9.85	10.49	11.11
	B	121	8.84	9.41	10.16	10.95	11.63
18	G	86	10.15	10.[illegible]	11.10	11.84	12.70
	B	118	10.18	10.88	11.81	12.60	13.30
24	G	85	11.00	11.50	12.38	13.14	14.16
	B	120	10.99	11.80	12.82	13.63	14.48
36	G	83	[illegible].90	13.42	14.33	15.30	17.00
	B	120	12.90	13.64	14.80	15.70	16.80
Length in cm							
1	G	85	51.3	52.9	53.8	55.2	56.5
	B	114	52.2	53.1	54.6	56.0	57.1
3	G	87	57.5	58.4	60.0	61.3	62.6
	B	120	58.7	59.7	61.5	62.8	64.0
6	G	88	63.5	65.2	66.3	67.8	69.3
	B	120	65.6	66.5	67.9	69.3	70.5
9	G	88	68.2	69.5	71.1	73.1	74.0
	B	121	70.0	70.9	72.3	73.6	75.0
12	G	87	72.5	73.2	75.1	76.9	78.1
	B	121	73.6	74.7	76.4	78.0	79.2
18	G	86	78.7	80.5	83.0	84.2	86.2
	B	118	80.0	[illegible]7	83.3	85.3	87.0
24	G	85	84.2	85.8	87.5	90.2	91.8
	B	120	85.0	87.3	88.9	90.9	92.8
36	G	82	92.1	94.2	96.2	99.0	100.8
	B	114	93.4	95.3	97.3	100.6	102.6
Crown-rump length in cm							
1	G	83	34.0	35.0	35.8	37.0	37.7
	B	114	34.3	35.3	36.5	37.5	38.5
3	G	87	38.3	39.3	40.3	41.4	42.2
	B	120	39.1	40.2	41.0	42.0	43.1
6	G	89	41.8	42.1	44.0	45.0	46.0
	B	120	43.1	43.8	44.7	46.0	46.8
9	G	88	44.5	45.3	46.3	47.3	48.6
	B	121	46.2	46.3	47.1	49.1	49.3
12	G	87	46.4	47.4	48.6	49.6	50.2
	B	121	46.9	47.7	49.0	50.1	51.0
18	G	83	48.4	50.5	51.9	52.8	53.8
	B	118	49.7	51.1	51.9	52.8	54.4
24	G	84	50.9	52.1	53.8	54.9	56.7
	B	119	51.5	53.0	54.3	55.5	57.0
36	G	80	54.8	56.2	56.8	58.3	59.5
	B	112	54.7	55.6	5[illegible]	59.3	60.9
Head circumf. in cm							
1	G	[illegible]	35.0	35.6	36.2	36.7	37.6
	B	114	35.5	36.2	37.0	37.8	38.6
3	G	87	37.9	38.7	39.5	40.3	40.4
	B	120	38.6	39.5	40.3	41.0	41.7
6	G	88	40.9	41.5	42.3	42.8	43.4
	B	120	41.9	42.7	43.3	44.0	44.8
9	G	88	42.7	43.3	44.0	44.5	45.5
	B	121	43.7	44.5	45.0	45.8	46.6
12	G	[illegible]	44.0	44.5	45.3	45.9	46.6
	B	121	45.0	45.8	46.5	47.2	47.7
18	G	86	45.4	45.9	46.7	47.3	48.2
	B	118	46.4	47.1	48.1	49.0	49.6
24	G	85	46.4	46.8	47.8	48.3	49.0
	B	120	47.3	48.1	48.9	49.7	50.5
36	G	83	47.1	47.8	48.8	49.5	50.1
	B	120	48.0	49.3	50.0	50.9	51.7
Chest circumf. in cm							
1	G	85	32.3	33.2	34.2	35.0	35.8
	B	114	32.4	33.4	34.6	36.2	37.0
3	G	87	36.4	37.5	38.8	40.0	41.3
	B	120	36.6	38.0	39.0	40.7	42.1
6	G	88	40.4	42.0	43.3	44.3	45.8
	B	120	40.7	42.0	43.3	45.0	46.7
9	G	88	42.5	44.0	46.2	46.5	47.7
	B	121	42.9	44.3	45.7	46.7	48.5
12	G	87	42.9	45.5	47.0	48.8	49.7
	B	121	44.7	46.0	47.4	49.0	50.3
18	G	85	45.5	46.5	47.6	49.8	51.3
	B	118	46.2	47.7	49.3	50.8	52.6
24	G	85	46.5	47.9	49.2	50.3	52.2
	B	120	47.0	48.8	50.2	51.9	53.3
36	G	81	48.8	50.2	51.2	52.3	54.0
	B	119	49.0	50.7	52.3	53.7	56.0
Upper arm circumf. in cm							
1	G	85	9.5	9.9	10.2	10.8	11.3
	B	114	9.4	9.7	10.2	11.0	11.6
3	G	84	11.0	11.7	12.5	13.1	13.5
	B	114	11.6	11.7	12.3	13.5	14.3
6	G	[illegible]	12.7	13.3	14.1	15.0	15.8
	B	113	12.8	13.3	14.1	15.3	15.5
9	G	83	13.7	14.3	14.7	15.5	16.6
	B	119	13.7	14.3	14.9	15.7	16.5

Appendix (*cont.*)

Age in mos	Sex	No	Skinfold measurements: Biceps in mm Mean	s.D.	Triceps in mm Mean	s.D.	Subscap in mm Mean	s.D.	Subiliac in mm Mean	s.D.
1–3	G	81	1.8	1.1	2.5	1.7	1.6	1.5	[illegible]	1.9
	B	105	1.7	1.0	2.6	1.6	1.4	1.6	2.5	1.7
3–6	G	78	1.3	1.6	2.1	1.9	0.3	1.3	−0.[illegible]	[illegible]
	B	104	1.2	1.5	1.9	1.7	0.3	1.8	1.3	[illegible]
6–9	G	78	−0.5	1.5	−0.1	1.7	−0.3	1.5	−1.3	1.9
	B	106	−0.4	1.1	0.4	1.7	0.1	1.5	−1.1	2.0
9–12	G	76	−0.2	0.8	−0.2	1.7	−0.3	1.1	−0.4	1.4
	B	118	−0.02	1.0	−0.1	1.8	−0.01	1.6	−0.4	1.6
12–18	G	72	−0.3	0.8	0.3	1.6	−0.5	1.3	−0.4	1.1
	B	108	−0.2	0.9	0.3	1.7	−0.3	1.5	−0.4	1.3
18–24	G	66	0.0	0.9	0.2	1.6	−0.5	1.1	−0.03	1.4
	B	98	0.1	0.7	0.0	1.7	−0.4	1.4	0.3	1.7
24–30	G	72	0.3	1.5	0.0	2.1	−0.1	1.7	0.1	1.4
	B	108	−0.2	1.0	−0.1	1.7	−0.7	1.1	−0.[illegible]	1.7

Appendix 3 (cont.)

Age in mos	Sex	No.	Percentiles 10	25	50	75	90
Skinfold measurements Biceps in mm							
1	G	85	3.1	3.3	3.8	4.2	4.7
	B	114	2.8	3.0	3.6	4.0	4.4
3	G	84	4.2	4.7	5.4	6.2	7.0
	B	114	3.9	4.5	5.3	6.0	[illegible]
6	G	85	5.3	6.2	6.8	7.4	8.7
	B	113	4.8	[illegible]	6.4	7.3	8.2
9	G	83	5.0	5.4	6.1	7.1	7.8
	B	116	4.4	5.2	5.6	7.0	7.5
12	G	82	4.9	5.4	6.0	6.8	7.8
	B	120	4.6	5.0	5.8	7.0	7.6
18	G	75	4.0	5.3	5.9	6.8	7.8
	B	110	4.4	5.0	5.6	6.6	7.2
24	G	78	4.5	5.1	5.9	[illegible]	7.7
	B	112	4.4	5.1	5.9	6.7	7.4
36	G	80	4.7	5.3	6.3	6.9	7.6
	B	114	4.4	5.0	5.8	6.3	7.3
Skinfold measurements Triceps in mm							
1	G	85	4.5	5.2	5.8	6.7	7.6
	B	114	4.0	4.7	5.3	6.3	7.0
3	G	[illegible]	6.2	7.2	8.2	9.2	10.5
	B	114	6.0	6.8	8.1	9.2	10.3
6	G	[illegible]	8.2	9.0	10.4	11.3	12.7
	B	113	7.8	8.6	9.7	11.1	11.8
9	G	83	7.9	[illegible]	10.1	11.2	12.5
	B	116	7.5	8.7	9.9	11.2	12.6
12	G	[illegible]	7.8	8.7	9.8	11.2	12.2
	B	120	7.8	[illegible]	9.8	11.1	12.2
18	G	75	7.9	8.9	10.3	11.3	12.3
	B	110	7.7	8.8	9.9	11.4	12.2
24	G	78	8.2	9.3	10.1	11.6	12.8
	B	111	7.4	8.5	9.8	11.6	13.1
36	G	79	8.2	9.4	10.3	11.8	12.5
	B	113	7.8	9.0	9.8	11.0	12.2
Skinfold measurements Subscap. in mm							
1	G	83	4.9	5.4	6.2	7.0	7.9
	B	114	4.2	4.6	5.6	6.5	7.8
3	G	84	5.9	6.9	8.0	8.6	9.4
	B	114	4.9	5.9	[illegible]	8.1	9.0
6	G	83	[illegible]	[illegible]	8.1	8.9	10.3
	B	113	5.5	6.2	7.1	8.4	10.1
9	G	82	6.0	6.7	7.8	8.8	10.1
	B	119	5.3	[illegible]	7.1	8.5	9.7
12	G	81	6.0	6.5	7.5	8.7	[illegible]
	B	120	5.3	6.0	7.2	8.6	9.6
18	G	75	5.7	[illegible]	7.1	8.0	9.0
	B	110	[illegible]	6.0	[illegible]	7.9	9.3
24	G	78	5.3	5.8	6.5	7.3	8.4
	B	111	4.6	5.4	6.5	7.4	8.3
36	G	79	4.7	[illegible]	6.1	7.3	8.6
	B	112	4.5	5.0	5.5	6.4	7.1
Skinfold measurements Suprailiac. in mm							
1	G	83	3.3	3.7	4.3	5.0	6.2
	B	113	2.8	3.3	4.1	4.8	5.4
3	G	84	5.1	5.9	7.3	8.2	9.4
	B	113	4.2	5.0	6.4	7.6	8.7
6	G	85	4.9	5.8	6.7	8.9	9.5
	B	113	4.3	4.9	[illegible]	7.8	9.2
9	G	83	4.2	4.7	5.7	6.6	7.6
	B	119	3.6	4.3	5.2	6.1	8.2
12	G	82	3.8	4.6	5.3	6.2	6.7
	B	120	3.7	4.1	4.8	6.0	7.3
18	G	75	3.6	4.2	4.9	5.7	6.6
	B	110	3.4	4.0	4.6	5.4	6.0
24	G	76	3.6	4.1	4.9	5.5	6.6
	B	112	3.2	3.8	4.5	5.9	6.4
36	G	79	3.8	4.3	4.8	5.5	6.4
	B	112	3.4	3.7	4.4	5.1	5.7
Anterior fontanel in cm							
1	G	81	2.0	2.0	2.9	3.8	4.0
	B	110	2.0	2.3	3.0	3.5	3.8
3	G	81	1.6	2.5	2.8	3.0	3.5
	B	109	1.4	2.0	2.5	3.0	3.8
6	G	[illegible]	1.0	1.8	2.0	3.0	3.4
	B	107	1.0	1.8	2.0	3.0	3.8
9	G	81	0.5	1.0	1.8	2.5	3.0
	B	117	0.2	1.0	1.5	2.5	3.0
12	G	83	[illegible]	0.0	1.0	2.0	2.1
	B	120	0.0	0.0	1.0	1.5	2.5
18	G	78	0.0	0.0	0.0	0.5	1.0
	B	112	0.0	0.0	0.0	[illegible]	1.6

Appendix 3 *(cont.)*

Age in mos	Sex	N	10	25	50	75	90
			Percentiles				
12	G	84	14.1	14.6	15.3	15.9	16.8
	B	121	13.8	14.7	15.4	16.2	17.3
18	G	81	14.3	14.8	15.6	16.2	17.1
	B	113	14.4	15.0	15.7	16.6	17.5
24	G	83	14.6	15.0	15.8	16.5	17.3
	B	117	14.5	15.1	16.0	16.9	17.5
36	G	83	15.0	15.7	16.3	17.2	17.6
	B	119	15.1	15.7	16.4	17.0	[illegible]
C lf circumf in cm							
1	G	85	11.0	11.4	12.0	12.5	[illegible]
	B	114	10.7	11.2	11.9	[illegible]	13.5
3	G	84	13.5	14.2	14.9	15.5	16.3
	B	114	13.2	14.0	14.8	16.0	16.6
6	G	85	15.9	16.5	[illegible]	17.9	18.6
	B	113	15.5	16.1	17.2	18.3	19.0
9	G	83	17.0	17.7	18.5	19.1	19.7
	B	118	16.7	17.6	18.3	19.3	19.8
12	G	84	17.4	18.4	19.1	19.8	[illegible]
	B	121	17.5	18.1	19.1	19.9	20.8
18	G	82	18.5	19.4	19.9	20.6	21.5
	B	113	18.4	19.2	19.9	20.9	21.7
24	G	83	18.8	19.7	20.5	21.4	22.2
	B	117	18.5	19.6	20.5	[illegible]	22.1
36	G	83	20.0	20.5	21.3	[illegible]	[illegible]
	B	[illegible]	19.5	20.3	[illegible]	22.0	22.8
Bicondyl. femur in cm							
1	G	85	3.1	3.3	3.4	3.5	3.7
	B	114	[illegible]	3.3	3.5	3.7	4.0
3	G	84	3.7	3.9	4.1	4.4	4.6
	B	114	[illegible]	3.9	4.2	4.5	[illegible]
6	G	85	4.3	4.4	4.7	5.0	5.2
	B	113	4.3	4.5	4.8	5.1	5.5
9	G	83	4.6	4.8	5.0	5.1	5.4
	B	119	4.6	4.8	5.1	5.3	5.7
12	G	84	4.8	5.0	[illegible]	5.4	5.6
	B	121	4.8	5.0	5.3	5.5	5.8
18	G	78	5.2	5.3	5.5	5.7	6.0
	B	112	5.2	5.5	5.7	6.0	6.2
24	G	[illegible]	5.3	5.5	[illegible]	5.9	[illegible]
	B	117	5.5	5.6	5.9	6.1	6.5
36	G	[illegible]	5.6	5.8	6.0	6.3	6.5
	B	110	5.8	6.0	[illegible]	6.4	6.7
Bicondyl. humerus in cm							
1	G	85	2.1	[illegible]	[illegible]	2.5	2.6
	B	114	2.1	2.2	[illegible]	[illegible]	2.6
3	G	84	[illegible]	2.6	2.8	3.0	3.2
	B	114	[illegible]	[illegible]	2.9	3.1	3.3

Age in mos	Sex	No	10	25	50	75	90
			Percentiles				
6	G	85	2.9	3.0	3.1	3.3	3.6
	B	113	[illegible]	3.1	3.3	3.5	3.7
9	G	83	3.1	[illegible]	3.3	3.5	[illegible]
	B	118	3.1	3.3	3.5	3.7	3.9
12	G	84	[illegible]	3.4	3.5	3.7	3.9
	B	121	3.3	3.5	3.7	3.8	4.0
18	G	78	3.4	3.4	3.6	3.8	4.0
	B	112	3.5	3.6	3.8	4.0	4.1
24	G	82	3.4	3.5	[illegible]	3.8	4.0
	B	117	3.6	3.7	3.9	4.1	4.3
36	G	82	3.6	3.7	3.8	4.0	4.2
	B	119	3.7	3.9	4.0	4.1	4.3
Max. pelvic width in cm							
1	G	[illegible]	8.4	8.8	9.0	9.4	9.7
	B	114	8.5	8.9	9.3	9.8	10.0
3	G	[illegible]	10.1	10.5	10.9	[illegible]	11.6
	B	114	10.0	10.4	11.0	11.5	12.1
6	G	85	11.3	11.5	[illegible]	[illegible]	13.2
	B	113	11.3	[illegible]	[illegible]	[illegible]	13.4
9	G	83	11.8	[illegible]	12.8	13.2	13.7
	B	118	[illegible]	12.3	[illegible]	13.4	14.0
12	G	84	12.3	[illegible]	[illegible]	13.8	14.3
	B	[illegible]	12.5	12.9	13.3	13.9	14.4
18	G	[illegible]	13.0	13.5	14.0	14.5	15.0
	B	111	13.5	13.9	14.2	14.8	15.3
24	G	76	13.8	14.1	14.7	15.2	15.6
	B	114	14.0	14.4	14.9	15.4	16.0
36	G	81	15.0	15.5	16.0	16.5	17.0
	B	113	15.2	15.7	16.1	16.7	[illegible]
Biacromial in cm							
1	G	82	[illegible]	12.5	12.8	14.3	14.8
	B	113	[illegible]	12.5	14.0	14.7	[illegible]
3	G	[illegible]	14.6	15.3	16.0	16.5	[illegible]
	B	114	[illegible]	15.6	16.3	16.8	17.2
6	G	85	16.4	17.2	18.0	18.8	19.3
	B	113	17.1	17.5	18.1	18.8	19.7
9	G	83	18.0	18.5	19.2	20.0	[illegible]
	B	118	18.4	19.0	19.6	[illegible]	[illegible]
12	G	84	19.0	[illegible]	[illegible]	[illegible]	[illegible]
	B	121	[illegible]	19.7	[illegible]	[illegible]	[illegible]
18	G	76	20.0	20.8	[illegible]	[illegible]	[illegible]
	B	111	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
24	G	[illegible]	[illegible]	21.7	22.5	[illegible]	23.7
	B	113	[illegible]	[illegible]	22.5	[illegible]	[illegible]
36	G	80	22.3	[illegible]	[illegible]	[illegible]	[illegible]
	B	113	22.8	[illegible]	[illegible]	[illegible]	[illegible]

Appendix 4 (cont.)

Age in mos	Sex	No.	10	25	50	75	90
			Percentiles				
9–12	G	76	−0.5	0.1	0.5	0.9	1.1
	B	117	−0.5	0.0	0.5	1.0	1.4
12–18	G	74	−0.9	−0.3	0.2	0.8	1.3
	B	110	−0.8	−0.1	0.4	0.9	1.5
18–24	G	76	−0.7	−0.3	0.3	0.7	1.0
	B	107	0.3	0.2	0.2	0.6	1.0
24–36	G	90	0.2	0.0	0.4	1.0	1.4
	B	116	0.4	0.0	0.3	0.7	1.1
Calf circumf. in cm							
1–3	G	81	1.9	2.6	3.0	3.6	4.0
	B	103	1.8	2.3	3.0	3.7	4.3
3–6	G	76	1.3	1.9	2.3	2.9	3.5
	B	104	1.3	1.9	2.3	2.9	3.5
6–9	G	78	0.1	0.6	1.3	1.7	2.3
	B	103	0.2	0.6	1.3	1.7	2.0
9–12	G	76	0.3	0.2	0.7	1.1	1.7
	B	117	0.2	0.3	0.7	1.3	1.9
12–18	G	73	0.3	0.3	0.8	1.4	2.1
	B	110	0.1	0.3	0.9	1.5	2.2
18–24	G	77	0.5	0.1	0.5	1.1	1.6
	B	107	0.7	−0.2	0.3	0.9	1.2
24–36	G	90	0.1	0.3	0.7	1.4	1.9
	B	117	0.1	0.3	0.7	1.3	1.6
Bicondyl. femur in cm							
1–3	G	81	0.4	0.6	0.7	0.9	1.1
	B	103	0.3	0.5	0.7	0.9	1.2
3–6	G	76	0.1	0.4	0.6	0.6	0.9
	B	104	0.3	0.5	0.6	0.8	1.0
6–9	G	78	0.2	0.1	0.3	0.4	0.6
	B	106	0.1	0.1	0.2	0.5	0.6
9–12	G	76	0.1	0.1	0.2	0.4	0.5
	B	117	0.2	0.1	0.2	0.4	0.6
12–18	G	72	0.0	0.2	0.4	0.5	0.8
	B	109	0.0	[illegible]	0.4	0.5	0.8
18–24	G	75	0.2	0.0	0.1	0.3	0.4
	B	106	0.0	0.1	0.2	0.2	0.5
24–36	G	75	0.1	0.2	0.3	0.5	0.6
	B	116	0.0	0.2	0.3	0.5	0.6
Bicondyl. humerus in cm							
1–3	G	[illegible]	0.1	0.3	0.5	0.6	0.7
	B	105	0.2	0.3	0.5	0.7	0.8
3–6	G	78	0	0.1	0.3	0.5	0.6
	B	104	0.0	0.2	0.3	0.5	0.7
6–9	G	78	0.1	0.1	0.2	0.3	0.5
	B	103	0.2	0.1	[illegible]	0.3	0.5

Age in mos	Sex	No.	10	25	50	75	90
			Percentiles				
9–12	G	76	−0.2	0.0	0.1	0.2	0.4
	B	117	−0.1	0.0	0.1	0.3	0.4
12–18	G	72	−0.2	0.0	0.1	[illegible]	0.4
	B	109	−0.2	0.0	0.2	0.2	[illegible]
18–24	G	72	−0.2	−0.1	0.1	0.2	0.3
	B	106	0.2	−0.1	0.1	0.3	0.3
24–36	G	78	−0.1	0.0	0.2	0.3	0.4
	B	116	−0.1	0.0	0.1	[illegible]	0.4
Max. pelvic width in cm							
1–3	G	80	1.1	[illegible]	1.9	2.1	2.5
	B	105	1.1	1.3	1.8	[illegible]	2.6
3–6	G	78	0.5	0.8	1.1	1.6	2.1
	B	104	0.4	0.8	1.1	1.6	2.0
6–9	G	76	−0.1	0.3	0.7	1.0	1.5
	B	106	−0.3	0.3	0.7	0.9	1.4
9–12	G	76	0.3	0.2	0.5	0.9	1.0
	B	117	−0.4	0.1	[illegible]	0.9	1.3
12–18	G	71	−0.1	0.4	0.8	1.1	1.4
	B	106	0.1	0.5	1.0	1.3	1.8
18–24	G	90	−0.3	0.2	0.7	1.0	1.2
	B	102	−0.3	0.3	0.7	1.0	1.3
24–36	G	74	0.7	1.1	1.2	1.6	1.9
	B	100	0.6	1.0	1.3	1.5	1.9
Biacromial in cm							
1–3	G	90	1.0	1.6	2.1	2.5	[illegible]
	B	103	1.1	1.5	2.3	2.6	3.2
3–6	G	78	0.8	1.7	2.2	2.7	3.4
	B	104	1.1	1.5	2.1	2.8	3.4
6–9	G	76	0.0	0.7	1.3	2.3	2.8
	B	103	0.1	0.7	1.3	1.8	2.3
9–12	G	76	0.0	0.5	1.0	1.5	2.3
	B	117	−0.3	0.3	0.6	1.4	2.0
12–18	G	71	−0.7	0.4	1.1	1.6	2.4
	B	106	−0.3	0.6	1.2	1.7	2.5
18–24	G	90	0.3	0.4	1.0	1.5	2.0
	B	101	0.3	0.3	0.9	1.8	2.4
24–36	[illegible]	[illegible]	0.2	0.7	1.3	[illegible]	2.6
	B	108	0.5	0.8	1.4	2.1	2.5
Skinfold measurements. Biceps in mm							
1–3	G	[illegible]	0.5	1.0	1.5	2.3	3.0
	B	103	0.5	1.0	1.6	2.3	3.0
3–6	G	78	−0.7	0.5	1.2	1.9	2.8
	B	104	0.5	0.3	1.1	2.0	2.6
6–9	G	[illegible]	−2.2	−1.3	−0.4	0.4	1.1
	B	103	−1.6	−1.0	−0.4	0.3	1.0

Appendix 4 *Percentiles for increments between each age for each body measurement in girls and boys separately*

Age in mos	Sex	No	Percentiles 10	25	50	75	90
Weight in kg							
0–1	G	82	0 11	0.26	0.39	0.57	0 78
	B	113	0 03	0.20	0 42	0 64	0 80
1–3	G	81	1 0	1.53	1 76	2 00	_.19
	B	105	1.24	1 57	1 93	2.16	2.59
3–6	G	78	1 41	1 65	1.89	_.16	2.35
	B	104	1.29	1.53	1 78	_._3	2.57
6–9	G	78	0 94	1 12	1.34	1 63	1 92
	B	105	0 83	1 03	1.34	1 67	1.94
9–12	G	76	0 54	0 79	1 00	1 _5	1 42
	B	117	0.5	0 76	1 07	1.36	1 70
12–18	G	75	0 92	1 05	1.31	1 60	1.89
	B	108	0 89	1 17	1 49	1.90	_.20
18–24	G	76	0 53	0 74	1 19	1 51	1 93
	B	105	0 41	0 67	1 10	1 48	1 85
24–36	G	81	1.33	1 64	2.10	2.5	2 89
	B	1_0	1.30	1 53	1.96	2.20	_.65
Length in cm							
0–1	G	82	2 0	2 6	3.5	4 6	5 4
	B	113	1 6	_.5	3.5	4.3	5.0
1–3	G	81	4.7	5.3	6.1	7 0	7 7
	B	105	5 0	6 1	6.9	7 8	8 6
3–6	G	78	4 6	5 7	6.5	7.5	8.1
	B	104	4 8	5 4	6.5	7.5	8.7
6–9	G	78	3.3	4 3	4 6	5 4	6.1
	B	103	3.3	3.8	4 4	5.0	[illegible]
9–12	G	76	3 0	3 5	4 0	4 7	5 7
	B	117	2.7	3._	4 1	4.8	5.3
12–18	G	75	5 4	6 4	7.2	8.0	8.8
	B	110	5 1	6 0	7 1	8 0	9 1
18–24	G	76	4 0	4 7	5 4	6.7	7 3
	B	107	3.7	4 7	5.5	6.4	7 1
24–36	G	79	6.6	7 7	8.6	9 4	9 9
	B	114	6 6	7 8	8 6	9 6	10.6
Crown-rump length in cm							
1–3	G	81	2.9	3 8	4.5	5 0	5 7
	B	105	3.5	4 1	4 9	5.4	6 1
3–6	G	78	2.0	_9	3.7	4 4	5.0
	B	104	2.2	3 0	3.6	4.5	5.3
6–9	G	78	0 5	1.5	2.4	3.2	4 1
	B	106	0 9	1 7	2.4	3 1	3.6
9–12	G	76	0 9	1 5	1 9	2 6	3.4
	B	116	0 4	1 1	1 6	_.3	3.0
1_–18	G	72	1 7	2.4	3.0	3.7	4 4
	B	109	1 4	2.4	3.2	4 0	4.5
18–_4	G	69	0.5	1.5	_.2	_.7	3.5
	B	100	0.8	1.5	2.2	2.8	3 4
_4–36	G	77	1.9	_.5	3.1	3.9	4.3
	B	11_	_.0	_6	3._	4 0	4 9
Head circumf in cm							
0–1	G	82	1.5	2.6	3.3	4 0	4 7
	B	113	2.0	_.5	3.6	4.3	[illegible]
1–3	G	81	_.5	2.6	3.1	3.4	3.8
	B	104	_4	2.8	3.3	3._	4._
3–6	G	78	2.3	2.5	_.9	3.2	3.4
	B	104	2.2	2.6	3.0	3.3	4 0
6–9	G	78	1 4	1 6	1 9	_._	_.5
	B	106	1.3	1 6	1.9	2 1	_.3
9–12	G	76	0 8	1 0	1.2	1 6	1 7
	B	117	0 8	1 0	1.3	1 6	1.8
12–18	G	74	0 7	1 1	1.5	1 7	1 9
	B	109	1 0	1.3	1 6	1 8	2.1
18–24	G	72	0.5	0 7	0.9	1 2	1.5
	B	106	0.2	0 6	0 9	1.3	1 7
24–36	G	81	0.5	0 8	1 1	1 3	1 6
	B	1_0	0.5	0 7	1 0	1.3	1.5
Chest circumf in cm							
1–3	G	81	2.6	3 6	4.8	5 7	6.4
	B	105	_.8	3.5	4.5	5.9	7.2
3–6	G	78	_.0	3._	4 4	5.8	6 7
	B	104	1 9	2.9	3 9	5 7	7._
6–9	G	78	−0._	0 6	_.0	2.4	4.5
	B	106	0.1	0.8	1 9	3 1	4 0
9–12	G	76	−0 4	0 5	1 5	2.3	3.5
	B	117	−0.2	0.5	1 7	_.9	4.3
12–18	G	_5	−0.2	0.5	1.3	_.3	2.4
	B	110	0 1	1 0	1.9	3 2	4 1
18–24	G	74	−0.9	0.1	1 4	2.6	3.0
	B	106	−0 9	−0 1	0 8	_.1	2.0
_4–36	G	79	−0 4	1 4		3 1	3.8
	B	119	−0.1	1 1	_.0	_.8	3.8
Upper arm circumf in cm							
1–3	G	81	0.5	1.5	_1	2 7	3 1
	B	105	0 8	1.5	2 1	_9	3 5
3–6	G	78	0.7	1 2	1 7	2 5	3.1
	B	104	0.4	1 2	1 6	2 3	_8
6–9	G	_8	−0 4	0 3	0 8	1 3	1 8
	B	106	−0.3	0 3	0 6	1 4	1 6

Appendix 4 (cont.)

Age in mos	Sex	No.	Percentiles 10	25	50	75	90
9–12	G	76	−0.5	−0.1	0.6	[illegible]	1.1
	B	117	−0.5	0.0	0.6	1.0	1.4
12–18	G	74	0.1	0.2	0.3	0.6	1.3
	B	110	0.0	0.1	0.4	0.9	1.5
18–24	G	76	0.7	0.3	0.3	0.7	1.0
	B	107	0.3	0.2	0.3	0.6	1.0
24–36	G	80	0.2	0.0	0.4	1.0	1.4
	B	116	0.4	0.6	0.3	0.7	1.1

Calf circumf. in cm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	81	1.9	2.5	3.0	3.6	4.0
	B	103	1.9	2.3	3.0	3.7	4.3
3–6	G	[illegible]	1.3	1.9	2.3	2.9	3.5
	B	104	1.3	1.8	2.3	2.9	3.5
6–9	G	78	0.1	0.6	1.2	1.7	2.3
	B	103	0.2	0.6	1.2	1.7	2.0
9–12	G	76	0.3	0.2	0.7	1.1	1.7
	B	117	−0.3	0.2	0.7	1.3	1.9
12–18	G	73	0.3	0.3	0.9	1.4	2.1
	B	110	0.1	0.3	0.9	1.5	2.2
18–24	G	77	0.5	0.1	0.5	1.1	1.8
	B	107	0.7	0.2	0.3	0.9	1.2
24–36	G	80	0.1	0.3	0.7	1.4	1.9
	B	117	0.1	0.3	0.7	1.2	1.6

Bicondyl. femur in cm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	[illegible]	0.4	0.6	0.7	0.9	1.1
	B	103	0.3	0.6	0.7	0.9	1.2
3–6	G	78	0.1	0.4	0.6	0.8	0.9
	B	104	0.3	0.5	0.6	0.8	1.0
6–9	G	78	0.2	0.1	0.3	0.4	0.6
	B	106	0.1	0.1	0.2	0.5	0.6
9–12	G	76	0.1	0.1	0.2	0.4	0.5
	B	117	0.2	0.1	0.2	0.4	0.6
12–18	G	72	0.0	0.2	0.4	0.6	0.6
	B	109	0.0	0.2	0.4	0.5	0.6
18–24	G	72	0.2	0.0	0.1	0.3	0.4
	B	106	0.0	0.1	0.2	0.2	0.5
24–36	G	78	0.1	0.2	0.3	0.5	0.6
	B	116	0.0	0.2	0.3	0.3	0.6

Bicondyl. humerus in cm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	[illegible]	0.1	0.3	0.6	0.6	0.7
	B	103	0.2	0.3	0.5	0.7	0.8
3–6	G	78	0.0	0.1	0.3	0.5	0.6
	B	104	0.0	0.2	0.3	0.3	0.7
6–9	G	78	0.1	0.1	0.2	0.3	0.5
	B	103	0.2	0.1	0.2	0.3	0.5

Age in mos	Sex	No.	Percentiles 10	25	50	75	90
9–12	G	76	−0.3	0.0	0.1	0.3	0.4
	B	117	−0.1	0.0	0.1	0.3	0.4
12–18	G	72	−0.3	0.0	0.1	0.3	0.4
	B	109	−0.3	0.0	0.2	0.3	0.5
18–24	G	72	−0.3	−0.1	0.1	0.3	0.3
	B	106	−0.3	−0.1	0.1	0.3	0.3
24–36	G	78	−0.1	0.0	0.2	0.3	0.4
	B	116	−0.1	0.0	0.1	0.3	0.4

Max. pelvic width in cm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	80	1.1	1.5	1.9	2.1	2.5
	B	103	1.1	1.3	1.8	2.3	2.6
3–6	G	78	0.6	0.8	1.1	1.5	2.1
	B	104	0.4	0.8	1.1	1.6	2.0
6–9	G	78	−0.1	0.2	0.7	1.0	1.5
	B	106	−0.3	0.3	0.7	0.9	1.4
9–12	G	76	−0.3	0.2	0.5	0.9	1.0
	B	117	−0.4	0.1	0.6	0.9	1.3
12–18	G	71	0.1	0.4	0.8	1.1	1.4
	B	108	0.1	0.5	1.0	1.3	1.8
18–24	G	[illegible]	0.3	0.2	0.7	1.0	1.3
	B	102	−0.3	0.3	0.7	1.0	1.3
24–36	G	74	0.7	1.1	1.3	1.6	1.9
	B	109	0.6	1.0	1.3	1.5	1.9

Biacromial in cm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	80	1.0	1.6	2.1	2.5	2.9
	B	103	1.1	1.5	2.3	2.8	3.2
3–6	G	78	0.8	1.7	[illegible]	2.7	3.4
	B	104	1.1	1.5	2.1	2.8	3.4
6–9	G	78	0.0	0.7	1.3	2.2	2.6
	B	106	0.1	0.7	1.3	1.8	2.3
9–12	G	76	0.0	0.3	1.0	1.3	2.3
	B	117	−0.3	0.3	0.8	1.4	2.0
12–18	G	71	0.3	0.4	1.1	1.8	2.4
	B	108	0.3	0.6	1.3	1.7	2.8
18–24	G	[illegible]	0.3	0.4	1.0	1.3	2.0
	B	101	[illegible]	0.3	0.9	1.8	2.4
24–36	G	72	0.3	0.7	1.3	1.8	2.8
	B	109	0.6	0.8	1.4	2.1	2.5

Skinfold measurements. Biceps in mm

Age in mos	Sex	No.	10	25	50	75	90
1–3	G	81	0.8	1.0	1.5	2.3	3.0
	B	103	0.8	1.0	1.6	2.3	3.0
3–6	G	78	0.7	0.5	1.3	1.9	2.8
	B	104	0.6	0.3	1.1	2.0	2.6
6–9	G	78	−2.2	−1.3	0.4	0.5	1.1
	B	103	−1.6	−1.0	0.4	0.3	1.0

APPENDIX 4 *Percentiles for increments between each age for each body measurement in girls and boys separately*

Age in mos	Sex	No	10	25	50	75	90
Weight in kg							
0–1	G	[illegible]	0.11	0.26	0.39	0.57	0.78
	B	113	0.03	0.20	0.42	0.64	0.80
1–3	G	81	1.20	1.53	1.75	2.00	[illegible]
	B	103	[illegible]	1.57	1.93	2.15	2.59
3–6	G	78	1.41	1.63	1.89	[illegible]	[illegible]
	B	104	1.29	1.53	1.78	2.23	2.57
6–9	G	78	0.94	1.12	1.34	1.63	1.92
	B	105	0.82	1.03	1.34	1.6	1.94
9–12	G	76	0.54	0.79	1.00	1.25	1.42
	B	117	0.52	0.76	1.07	1.36	1.70
12–18	G	75	0.92	1.05	1.31	1.60	1.89
	B	108	0.89	1.17	1.49	1.90	.20
18–24	G	76	0.53	[illegible]	1.19	1.51	1.93
	B	105	0.41	0.67	1.10	1.48	1.85
24–36	G	81	1.33	1.64	2.10	2.52	2.89
	B	120	1.30	1.53	1.96	2.20	[illegible]
Length in cm							
0–1	G	82	2.0	2.6	3.5	4.6	5.4
	B	113	1.6	2.5	3.5	4.3	5.0
1–3	G	81	4.7	5.3	6.1	7.0	7.7
	B	105	5.0	6.1	6.9	7.8	8.6
3–6	G	78	4.6	5.7	6.5	7.5	8.1
	B	104	4.8	5.4	6.5	7.5	8.7
6–9	G	78	3.3	4.2	4.6	5.4	6.1
	B	105	3.3	3.8	4.4	5.0	5.9
9–12	G	76	3.0	3.5	4.0	4.7	5.7
	B	117	2.7	3.2	4.1	4.8	5.2
12–18	G	75	5.4	6.4	7.2	8.0	8.8
	B	110	5.1	6.0	7.1	8.0	9.1
18–24	G	76	4.0	4.7	5.4	6.7	7.2
	B	107	3.7	4.7	5.5	6.4	7.1
4–36	G	79	6.8	7.7	8.6	9.4	9.9
	B	114	6.6	7.6	8.6	9.6	10.5
Crown–rump length in cm							
1–3	G	81	2.9	3.8	4.5	5.0	5.7
	B	105	3.5	4.1	4.9	5.4	6.1
3–6	G	78	2.0	2.9	3.7	4.4	5.0
	B	104	2.2	3.0	3.6	4.5	5.3
6–9	G	78	0.5	1.5	[illegible]	3.2	4.1
	B	106	0.9	1.7	2.4	3.1	3.6
9–12	G	76	0.9	1.5	1.9	2.6	3.4
	B	116	0.4	1.1	1.6	2.3	3.0
12–18	G	73	1	2.4	3.0	3.7	4.4
	B	109	1.4	2.4	3.2	4.0	4.5

Age in mos	Sex	No	10	25	50	75	90
18– 4	G	69	0.5	1.5	2.2	[illegible]	3.5
	B	100	0.8	1.5	2.2	[illegible]	3.4
24–36	G	77	1.9	2.5	3.1	3.9	4.3
	B	113	2.0	2.6	[illegible]	4.0	4.9
Head circumf in cm							
0–1	G	8	1.5	2.6	3.3	4.0	4.7
	B	113	2.0	2.5	3.6	4.3	5.3
1–3	G	81	[illegible]	2.6	3.1	3.4	[illegible]
	B	104	[illegible]	2.8	3.3	3.7	4.2
3–6	G	78	2.3	[illegible]	2.8	3.2	3.4
	B	104	2.2	[illegible]	3.0	3.3	4.0
6–9	G	78	1.4	1.6	1.9	2.2	[illegible]
	B	106	1.3	1.6	1.9	2.1	[illegible]
9–12	G	76	0.8	1.0	[illegible]	1.6	1.7
	B	117	0.8	1.0	1.3	1.6	1.8
12–18	G	74	0.7	1.1	1.5	1.7	1.9
	B	109	1.0	1.3	1.6	1.8	1
18–24	G	72	0.5	0.	0.9	1.2	1.5
	B	106	0.2	0.6	0.9	1.3	1.7
4–36	G	81	0.5	0.8	1.1	1.3	1.6
	B	120	0.5	0.7	1.0	1.3	1.5
Chest circumf in cm							
1–3	G	81	2.6	3.6	4.8	5.7	6.4
	B	105	2.8	3.5	4.5	5.9	[illegible]
3–6	G	78	2.0	[illegible]	4.4	5.5	6.7
	B	104	1.9	2.9	3.9	5.7	7.2
6–9	G	78	[illegible]	0.6	[illegible]	2.4	4.5
	B	106	0.1	0.6	1.9	3.1	4.0
9–12	G	76	−0.4	0.5	1.5	[illegible]	3.5
	B	117	[illegible]	0.5	1.7	[illegible]	4.2
12–18	G	75	[illegible]	0.5	1.2	[illegible]	3.4
	B	110	0.1	1.0	1.9	[illegible]	4.1
18–24	G	4	−0.9	0.1	1.4	2.6	3.0
	B	106	−0.9	−0.1	0.6	2.1	3.0
24–36	G	79	−0.4	1.4	2.2	3.1	3.8
	B	119	−0.1	1.1	2.0	[illegible]	3.8
Upper arm circumf in cm							
1–3	G	81	0.5	1.6	2.1	2.7	3.1
	B	103	0.9	1.3	2.1	2.9	3.5
3–6	G	78	0.7	1.2	1.7	2.5	3.1
	B	104	0.4	1.2	1.6	2.3	2.8
6–9	G	76	−0.4	0.3	0.8	1.3	1.8
	B	106	−0.3	0.3	0.8	1.4	1.8

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The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study

II Data on the Mental Development During the first Five Years

(as measured by Brunet Lézine Psychomotor Development Test and Terman-Merrill Intelligence Test)

by INGRID KLACKENBERG-LARSSON and JAN STENSSON

This paper presents some data concerning the mental development of children from 3 months to 5 years of age obtained in a longitudinal study on the development of Swedish children in an urban district.

The sample is composed of 212 children (122 boys and 90 girls) from Solna a town near Stockholm for which area it is found t have good representativeness. (For information regarding the general outline of the longitudinal study and the representativity and social composition of the sample see Papers I and II of our series [10 11])

Thi Swedish study forms a link in a group of international studies, coordinated by International Children s Centre in Paris.

Test Methods and Procedures

In accordance w th the established base line for these coordinated growth studies, the ch ldren were tested on ight occasions t the ages of 3 6, 9 1., 18 and 4 months by Brunet Lézine s psychomotor dev lopment test [4 5], a French adaptation of Gesell' development schedule and at 3 and 5 years with the Terman Merrill intelligence test (1937 revised edition Form L) [13]

The Brunet-Lézine test consists of 10 items at each age Four of them consist of questions to the mother about the child s bilities.

A total development quotient is computed as well as quotients for four subscales. a) Motor development b) Coordination development, c) Language development and d) Social Personal development.

Language items in Terman-Merrill have been analysed separately Further the language development up to 5 years has been studied by means of ratings (see Appendix 1)

In tests on children up to 2 years of age the mother or substitute (in a few cases) was always present. At 3 years the child was tested at one end of the room, while its mother was interviewed by another psychologist at the other end, because of the difficulties of separating a child from its mother at this early age

At 5 years mother and child were separated, generally without any difficulty

Appendix 4 (*cont*)

Age in mos	Sex	No	Percentiles 10	5	50	75	90
9–1	[illegible]	74	−1	−0.6	−0.2	0.3	0.8
	B	116	−1.0	−0.6	−0.2	0.6	1.2
12–18	G	68	−1.3	−0.6	−0.1	0.[illegible]	0.9
	B	10	−1.4	−0.9	−0.[illegible]	0.4	0.9
18–24	G	6	−1.0	−0.7	−0.1	0.5	1.2
	B	100	−0.5	−0.[illegible]	0.1	0.6	0.9
4 36	G	72	−0.8	−0.5	0.1	0.7	1.4
	B	108	−1	−0.7	−0.2	0.3	0.8
Ski fold measurements Triceps in mm							
1–3	G	81	0.1	1.4	2.5	3.4	4.4
	B	103	0.7	1.5	[illegible].5	3.6	4.7
3–6	G	78	−0.1	0.7	2.1	3.3	4.4
	B	104	−0.1	0.6	1.8	.6	3.6
6–9	G	78	−2.2	−1.1	−0.3	0.8	1.6
	B	105	−1.7	−0.7	0.3	1.4	6
9–12	G	74	−2.4	−1.4	−0.2	1.0	2.1
	B	116	−2.4	−1.5	0.0	1.3	2.4
12–18	G	68	−2.2	−0.9	0.2	1.3	2.1
	B	10	−2.0	−1.0	−0.1	1.4	[illegible].3
18–24	G	69	−[illegible].0	−0.8	0.1	1	[illegible].5
	B	99	−2.0	−1.3	0.0	1.[illegible]	4
4–36	G	72	−2.7	−1.2	0.3	1.3	[illegible].3
	B	107	−2.3	−1.2	−0.3	1.2	2.3
Skinfold measureme ts S bicep in mm							
1–3	G	[illegible]	−0	0.5	1.6	[illegible].6	3.4
	B	105	−0.5	0.2	1.4	2.2	3.1
3–6	G	78	−1.2	−0.6	0.[illegible]	1.1	2.0
	B	104	−1.5	−0.7	0	1	3
6–9	G	78	−2.0	−1.1	−0.[illegible]	0.5	1.[illegible]
	B	106	−1.5	−0.8	0.0	0.8	1.9
9–12	G	73	−1.6	−1.0	−0.3	0.4	1.1
	B	116	−1.4	−0.6	0.0	0.7	1.8

Age in mos	Sex	No	Percentiles 10	5	50	75	90
12–18	G	6	−2.1	−1.3	−0.6	0.2	1.5
	B	107	− 1	−1.0	−0.4	0.4	1.3
18–24	G	69	−1.6	−1.1	−0.6	0.[illegible]	0.9
	B	99	−1.7	−1	−0.5	0.2	0.9
24–36	G	72	−1.8	−0.9	−0.4	0.3	1.2
	B	106	−1.9	−1.[illegible]	−0.6	0.0	0.4
Skinfold measurements Subiliac in mm							
1–3	G	80	0.7	1.5	2.8	4.0	3.0
	B	104	0.4	1.2	2.6	[illegible]	4.5
3–6	G	78	−[illegible].3	−1.5	−0.3	0.8	2.[illegible]
	B	103	−2.[illegible]	−1.1	−0.2	1.2	2.7
6–9	G	[illegible]	−3.4	−1.8	−1.1	−0.6	0.4
	B	105	−3.3	−2.3	−1.0	0.0	1.1
9–1	G	4	−1.9	−1.1	−0.5	0.[illegible]	1.1
	B	116	−1.9	−0.9	−0.3	0.4	1.[illegible]
12–18	G	63	−[illegible].1	−1.0	−0.5	0.2	1.0
	B	107	−2.0	−0.9	−0.3	0.3	0.8
18– 4	G	68	−1.7	−0.7	−0.1	0.5	1.5
	B	100	−1.1	−0.6	−0.2	0.5	1.5
4–36	G	2	−1.6	−0.7	−0.1	0.7	1.5
	B	10	−1.4	−0.5	0.0	0.7	1.[illegible]
Anterior fontanel in cm							
1–3	G	77	−1.0	−0.5	−0.3	0.3	0.5
	B	99	−1.3	−0.7	−0.5	0.0	0.5
3–6	G	5	−1.2	−1.0	−0.5	0.0	0.5
	B	97	−1.0	−0.5	−0.5	0.0	0.5
6–9	G	75	−1.2	−1.0	−0.5	0.0	0.3
	B	99	−1.1	−1.0	−0.5	−0.5	0.0
9–1	G	73	−1.0	−1.0	−0.5	0.0	0.3
	B	116	−1.0	−1.0	−0.5	0.0	0.0
1 –18	G	70	−2.5	−1.5	−1.0	0.0	0.0
	B	108	−2.0	−1.5	−1.0	−0.3	0.0
18– 4	G	7	−1.0	−0.5	0.0	0.0	0.0
	B	107	−1.0	−0.3	0.0	0.0	0.0

DQs and IQs

Results

In the strictly longitudinal and the total sample the means and standard deviations for the raw quotients were calculated and the results are given in Table 2. As will be seen the means are almost identical.

Table shows that only at 24 months the mean quotient is about 100 and thus on the level with the norms of Brunet-Lézine and that at all other ages the obtained means are abo e these norms most markedly at 3 and 6 months (DQ = 114) and at 5 years of age (IQ = 111) (Terman-Merrill).

The standard deviations also vary at different ages. At 3 months nd 3 years the deviation is about 17 and varies from 9.5 to 1 between 6 months and years. The total quotients have therefore been scaled so that the means are 100 and the standard deviations 16 at all ages in order to facilitate comparisons over ages.

Because of the different loss in different social classes and sexes in the strictly longitudinal sample the total sample will form the main basis for the further analysis in this report.

Subscales Table a shows the raw mean quotients for 1) motor 2) coordination, 3) language and 4) personal-social development from 3 months to 4 months of age in th Brunet Lézine test A striking feature is the high level at 3 and 6 months of age within the motor and social spheres. The coordination scale is that in which the mean quotients are most uniform between the ages.

Frequencies of solution of the items in the Brunet Lé ine test The frequencies of sol tion of the items are on the whole very high. The median value in our sample is 78% compared with Brunet-Lézine's 68%. Several items seem to be placed at too high an age level for our children, e.g. "turning from supine to stomach" is placed at 8 months but 74% of our children can do this already at 6 months (26 weeks) by Gesell it is placed at 24 weeks. Such items as "to eat with spoon" and "to drink from cup" our children also perform at an earlier age than the French norms assume.

On the other hand, such an item as "to ask for the pot" has specially low frequency of solution. At 18 months of age it is solved only by 15% of our children. The items which seem to be most adequately placed for our children at all ages are the coordination items.

Discussion

When the Swedish study was planned, no infants scale was standardized for Swedish children and we therefore had to choose among tests from other countries. In the parallel European C.I.E. studies Brunet-Lézine [4] and Griffiths [1] tests were used.

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Recruitment from the beginning: Boys = 122, Girls = 90, Total = 212. C = completed, M = missed, U = unobtainable DQ and IQ s

Age — Sex and soc. class	3 mos			6 mos			9 mos			12 mos			18 mos			2 yrs			3 yrs			5 yrs		
	C	M	U	C	M	U	C	M	U	C	M	U	C	M	U	C	M	U	C	M	U	C	M	U
Boys	110	12	1	113	9	1	118	4	1	120	1	1	113	9		118	3	1	119	1	2	114	6	2
Girls	83	7		86	4		84	6		88	4		82	8		84	6		84	5	1	80	8	2
Total	193	19	1	199	13	1	*02	10	1	206	5	1	195	17		202	9	1	*03	6	3	194	14	4
Boys I	14	6		19	1		19	1		20			19	1		10	1		19	1		19	1	
II	46	4		46	4		48	2		49	1		45	5		52			52		1	54		1
III	50	1	1	48	3	1	51		1	51		1	49	3		47	2	1	48		1	41	5	1
Girls I	14	1		13	2		12	3		15			12	3		12	3		12	2	1	12	[illegible]	1
II	26	3		28	1		20	3		27	2		27	2		31	1		30	1		28	4	1
III	43	3		46	1		46			44	2		43	3		41	2		4[illegible]	2		40	2	
Total I	28	7		32	3		31	4		35			31	4		31	4		31	3	1	31	2	1
II	72	7		74	5		74	5		76	3		72	7		83	1		82	1	1	82	4	2
III	93	4	1	93	4	1	97		1	95	2	1	92	6		88	4	1	90	2	1	81	7	1

The Accomplishment of Planned Study

It is unavoidable in a study like the present one which covers an age period of [illegible] years that some children will leave the study and some will for various reasons be unable to come at all set ages for examination Consequently there have been some missed examinations among the different ages, as can be seen from Table 1 A strictly longitudinal group i.e a sample in which each child has been examined at each age from 3 months to 5 years, will thus be restricted to 85 boys and 55 girls, altogether 140 children (= 66 % of 212 children)

The loss in the strictly longitudinal sample is unevenly distributed over the social classes and differs between boys and girls as will be seen below

	Swedish social class (at one year)					
	Class I		Class II		Class III	
	n	%	n	%	n	
Boys	8	40	14	*8	15	*7
Girls	12	80	1	41	11	4
	*0	57	6	33	*6	*7

Calculations were therefore also made on a cross-sectional sample including all children tested at a certain age (in somewhat varying numbers n = 193–206) and here called the total sample

Five children in both samples in whom DQ and IQ were not obtained were excluded Four children in the strictly longitudinal sample who were tested beyond the internationally established time limits were also excluded These time limits are at 3 6 9 12 months ± 2 weeks, at 18 months 2 3 and 5 years ± 4 weeks

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In the strictly longitudinal and the total sample the means and standard deviations for the raw quotients were calculated and the results are given in Table 2a. As will be seen, the means are almost identical.

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Subscales. Table 3 shows the raw mean quotients for 1) motor, 2) coordination, 3) language and 4) personal-social development from 3 months to 24 months of age in the Brunet-Lézine test. A striking feature is the high level at 3 and 6 months of age within the motor and social spheres. The coordination scale is that in which the mean quotients are most uniform between the ages.

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When the Swedish study was planned, no infants' scale was standardized for Swedish children and we therefore had to choose among tests from other countries. In the parallel European C.I.E. studies Brunet-Lézine [4] and Griffiths [12] tests were used.

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Age ... Sex and soc class		3 mos C	3 mos M	3 mos U	6 mos C	6 mos M	6 mos U	9 mos C	9 mos M	9 mos U	12 mos C	12 mos M	12 mos U	18 mos C	18 mos M	18 mos U	2 yrs C	2 yrs M	2 yrs U	3 yrs C	3 yrs M	3 yrs U	5 yrs C	5 yrs M	5 yrs U
Boys		110	12	1	113	9	1	118	4	1	120	1	1	113	9		118	3	1	119	1		114	6	2
Girls		83	7		86	4		84	6		86	4		82	8		84	6		84	5	1	80	8	2
Total		[illegible]	19	1	199	13	1	202	10	1	206	5	1	195	17		202	9	1	203	6	3	194	14	4
Boys	I	14	6		19	1		19	1		20			19	1		19	1		19	1		19	1	
	II	46	4		46	4		48	2		49	1		45	5		52			5		1	54		1
	III	50	1	1	48	3	1	51		1	51		1	49	3		47	2	1	48		1	41	5	1
Girls	I	14	1		13	2		12	3		15			12	3		12	3		12	2	1	12	2	1
	II	26	3		28	1		26	2		27	2		27	2		31	1		30	1		28	4	1
	III	43	2		45	1		46			44	2		43	3		41	2		42	2		40	2	
Total	I	28	7		32	3		31	4		35			31	4		31	4		31	3	1	31	3	1
	II	72	7		74	5		74	5		76	3		72	7		83	1		82	1	1	82	4	2
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Boys	8	40	14	28	15	27
Girls	12	60	12	41	11	[illegible]
	20	57	26	33	[illegible]	[illegible]

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	III	50	1	1	48	3	1	51		1	51		1	49	2		47	2	1	48		1	41	5	1
Girls	I	14	1		13	2		12	2		15			12	2		12	2		12	2	1	12	2	1
	II	26	3		28	1		26	3		27	2		27	2		31	1		30	1		28	4	1
	III	43	3		45	1		46			44	2		43	3		41	2		42	2		40	2	
Total	I	28	7		32	3		31	4		35			31	4		31	4		31	3	1	31	2	1
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boys and girls of total and subquotients in the longitudinal and cross-sectional (=total samples from 6 months to 5 years

levels in this and the following tables = .05; ** = .01; = .001

		Brunet Lézine						Terman Merrill		
6 mos		12 mos		18 mos		2 yrs		3 yrs		5 yrs
85/55/140		85/85/140		85/55/140		85/55/140		84/56/140		85/55/140
Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean
104.5	8.5	108.1	11.8	103.6	9.4	96.0 **	9.2	101.2	16.1	109.4
108.3	9.0	108.2	11.1	106.7	8.1	104.1	9.4	105.3	15.3	111.1
105.9	9.5	108.1	11.4	104.9	9.0	100.8	9.2	102.8	15.8	110.1
116/84/202		120/86/206		113/82/195		118/84/202		119/84/203		114/80/194
104.5	9.8	108.7	11.8	103.6	9.3	98.6	8.9	102.1	16.7	110.8
108.0	9.4	107.9	10.8	107.4	9.0	103.6	8.6	106.3	17.3	111.3
106.1	9.5	108.4	11.3	105.2	9.4	100.7	9.5	103.9	17.0	110.9
107.4	17.1	108.3	21.8	111.6	17.5	104.7	16.1			
107.0	13.4	108.3	19.3	114.0	13.3	109.2	11.3			
107.2	15.6	108.3	20.3	112.3	15.0	106.6	12.8			
101.7	12.0	104.4	18.9	104.0	21.3	96.1	14.8			
103.3	10.6	106.0	12.5	107.2	13.9	99.7	9.9			
102.3	11.5	105.1	16.4	105.3	18.6	97.6	13.1			
106.6	23.0	108.0 *	17.7	96.6	** 16.5	96.0	16.8			
112.0	22.5	116.4	18.7	104.3	14.7	102.3	14.0			
109.2	22.8	111.5	18.5	99.7	15.7	99.0	15.1			
104.0	12.5	102.5	14.4	98.3 **	11.8	93.3 **	13.7			
104.4	13.1	105.9	12.0	103.6	12.1	104.8	16.1			
104.4	12.4	103.9	12.9	100.6	12.2	98.1	16.4			
99.1	15.9	99.1	16.3	97.3 **	15.9	96.4	** 16.1	98.0	15.8	99.6
101.6	16.8	101.4	15.0	103.0	16.2	104.9	16.1	102.4	16.2	100.6
100.1	16.4	100.0	16.0	99.9	16.9	100.0	16.0	99.9	16.1	100.0

there are no test items for 27 months; the next step is from now on 6 months instead of 3. Further if ...-year-old happens to solve an item on the 3-year level this is not counted in the subscales, which finish at ... years.

Regarding individual items, it cannot be expected that all will be given an optimal suitability in character and age level, especially when the test is worked out for another country. For clinical use in Swe-

TABLE 2b *Sex differences in Griff... social classes from 18 months to 3 ye...*

Class		18 mos		2 years		3 y...
		Mean	n	Mean	n	Mean
I+II	Boys	102.2	29	100.0	31	105....
	Girls	110.5	[illegible]	110.4	20	111....
III	Boys	96.4	26	97.7	45	94....
	Girls	100.5	24	101.1	26	102....
IV+V	Boys	85.0 *	45	92.5	42 *	93....
	Girls	102.2	38	104.7	38	97....

being more pronounced at one age than at another But from other points of view this uneven distribution of items between the different categories at different ages has some disadvantages. The correlations e.g between ages may be lowered by changes in the factor structure of the test

It seems that the personal-social subscale is heterogeneous According to the authors it includes consciousness of oneself relations to other persons, adaptation to social situations and the games played by the child Our children can for instance be very forward in one aspect of the personal social area and at the same time very backward in another For instance, 84 % of our 18-month-old children solve the item to imitate simple actions of an adult placed at 21 months while they show a low ability (16 %) to solve the 18-months item to ask for the pot (The toilet training in Sweden seems now-a days to start comparatively late probably because of the common use of paper diapers which facilitates the mothers work)

With regard to our high quotients at 3 and 6 months, it should be mentioned that Brunet and Lézine do not recommend the calculations of DQs before the age of 4 months They point out that the DQs will be too high owing to the fact that an addition of a 3-day credit for an item at an early age is proportionally greater than at a later age [4] The same tendency can be seen in the results from coordinated studies using Brunet Lézine test [8 27]

In conformity to Griffiths [12] we find high standard deviations at the earliest age. She considers this to be attributable partly to a purely statistical floor effect She therefore corrects her figures by adding eight weeks both to *the mental and the chronological* age during the first eight months.

The fact that DQs are lower at 2 years may partly be due to ceiling effects. The more advanced 18-month-old children have more and better chances of showing their ability than have the advanced 2 year olds. The clever 18-month-old baby may try items from 21 –4 and 30 months level. For the clever 2 year-old infant however

TABLE 2a *Means and standard deviations f[illegible]*

		Brunet Lézine			
	Age	3 mos		6 mos	
	n B/G/T	85/55/140		83/33/1[illegible]	
Longitudinal		Mean	s.D	Mean	s.D
Raw total quotients	Boys	113 0	19 0	113.7	[illegible]
	Girls	117 6	13.6	115.5	[illegible]
	Total	114.8	17.2	114 4	[illegible]
	n B/G/T	110/83/193		113 [illegible]	
Cross-sectional (= *total*)					
Raw total quotients	Boys	113 1	18.7	113.7	[illegible]
	Girls	117 1	14.0	115.3	[illegible]
	Total	114.8	16.9	114 4	[illegible]
Motor	Boys	117.[illegible]	32.6	116.3	[illegible]
	Girls	1 4.[illegible]	[illegible]	117.[illegible]	[illegible]
	Total	120.[illegible]	29.[illegible]	116.6	[illegible]
Coordination	Boys	104 7	22.0	107 9	[illegible]
	Girls	107 4	16.7	110.5	[illegible]
	Total	105.9	19 9	109.0	[illegible]
Language	Boys	101.2	36.1	111 1	[illegible]
	Girls	113.3	30.5	114.[illegible]	[illegible]
	Total	106 4	34.2	112.4	[illegible]
Personal social	Boys	1[illegible]0.1	5.6	116.8	[illegible]
	Girls	1 1 9	1 1	119.3	[illegible]
	Total	1[illegible]0.9	23 7	117 9	[illegible]
Scaled total quotients	Boys	98.4	17 7	99 1	[illegible]
	Girls	102.[illegible]	13.3	101 1	[illegible]
	Total	100 00	16.0	99 9	[illegible]

boys and girls of total and subquotients in the longitudinal and cross-sectional (=total) samples from 3 months to 6 years

levels in this and the following tables = .05; ** = .01; *** = .001

Brunet-Lézine								Terman-Merrill			
9 mos		12 mos		18 mos		2 yrs		3 yrs		5 yrs	
85/55/140		85/55/140		85/55/140		85/55/140		85/55/140		85/55/140	
Mean	s.D.	Mean	s.D.	Mean	s.D.	Mean	s.D.	Mean	s.D.	Mean	s.D.
104.8	8.8	104.1	11.6	102.8	9.4	98.6	9.2	101.2	16.1	109.4	14.2
106.3	[illegible]	108.2	11.1	106.7	8.1	104.1 *	8.4	105.3	16.2	111.1	10.7
105.2	8.5	106.9	11.4	104.9	9.0	100.8	[illegible]	102.8	15.9	110.1	12.9
118/84/202		120/86/206		113/82/195		116/84/202		119/84/203		114/80/194	
104.5	[illegible]	104.7	11.8	102.6	9.3	98.6	[illegible]	102.1	16.7	110.6	14.5
108.0	9.4	107.3	10.9	107.4 **	9.0	103.6 ***	9.9	106.5	17.2	111.5	12.6
106.1	9.5	105.6	11.2	105.2	9.4	100.7	9.5	103.8	17.0	110.9	13.7
107.4	17.1	108.5	21.6	111.0	17.8	104.7	15.1				
107.9	13.4	108.3	18.3	114.0	13.3	109.2	11.3				
107.5	15.6	106.9	20.2	112.3	15.9	106.8	13.8				
101.7	12.0	104.4	18.8	104.0	21.3	96.1	14.9				
103.2	10.8	106.0	12.2	107.2	13.9	98.7	9.9				
102.3	11.3	105.1	16.4	105.2	18.6	97.6	13.1				
105.5	23.9	108.6	17.7	96.5	15.8	96.0	16.9				
113.0	22.2	116.4 **	18.7	104.3 **	14.7	103.2 *	14.0				
109.2	22.8	111.6	18.5	99.7	15.7	99.0	16.1				
100.9	12.5	102.6	14.6	98.2	11.8	93.2	13.7				
108.4	12.1	105.9	13.0	103.6 **	12.1	104.8 **	16.1				
104.4	12.4	103.9	13.9	100.6	12.2	98.1	15.4				
99.1	18.9	98.1	18.8	97.2	16.9	96.4	15.1	98.0	15.2	99.6	16.9
101.6	18.9	101.4	18.0	102.6 **	16.2	104.8 **	16.1	102.5	16.2	100.6	14.7
100.1	18.9	100.0	18.0	99.9	16.9	100.0	16.0	99.9	16.1	100.0	16.0

there are no test items for 27 months; the next step is from now on 6 months instead of 3. Further, if a 2-year-old happens to solve an item on the 3-year level, this is not counted in the subscales, which finish at 2½ years.

Regarding individual items, it cannot be expected that all will be given an optimal suitability in character and age level, especially when the test is worked out for another country. For clinical use in Swe-

TABLE 2b *Sex differences in Griffiths social classes from 18 months to 3 years*

Class		18 mos Mean	n	2 years Mean	n	3 yrs Mean	n
I+II	Boys	102.2	29	100.0	31	106.1	35
	Girls	110.8	19	110.4	20	111.4	31
III	Boys	98.4	38	97.7	45	96.8	42
	Girls	100.5	24	101.1	28	102.2	24
IV+V	Boys	95.0	48	92.5	42	93.2	42
	Girls	102.2 *	39	104.7	38	97.9 *	39

being more pronounced at one age than at another. But from other points of view this uneven distribution of items between the different categories at different ages has some disadvantages. The correlations e.g. between ages, may be lowered by changes in the factor structure of the test.

It seems that the personal-social subscale is heterogeneous. According to the authors it includes consciousness of oneself, relations to other persons, adaptation to social situations and the games played by the child. Our children can for instance be very forward in one aspect of the personal-social area and at the same time very backward in another. For instance 84 % of our 18-month-old children solve the item "to imitate simple actions of an adult" placed at 21 months while they show a low ability (15 %) to solve the 18-months item "to ask for the pot". (The toilet training in Sweden seems now-a-days to start comparatively late, probably because of the common use of paper diapers which facilitates the mothers' work.)

With regard to our high quotients at 3 and 6 months it should be mentioned that Brunet and Lézine do not recommend the calculations of DQs before the age of 4 months. They point out that the DQs will be too high owing to the fact that an addition of a 3-day credit for an item at an early age is proportionally greater than at a later age [4]. The same tendency can be seen in the results from coordinated studies using Brunet-Lézine test [8, 27].

In conformity to Griffiths [12] we find high standard deviations at the earliest age. She considers this to be attributable partly to a purely statistical floor effect. She therefore corrects her figures by adding eight weeks both to the mental and the chronological age during the first eight months.

The fact that DQs are lower at 2 years may partly be due to ceiling effects. The more advanced 18-month-old children have more and better chances of showing their ability than have the advanced 2 year olds. The clever 18-month-old baby may try items from 21, 24 and 30 months level. For the clever 2 year-old infant, however

TABLE 2a. *Means and standard deviations [illegible]*

Significance [illegible]

		Brunet Lézine			
	Age	3 mos		6 mos	
	n B/G/T	85/55/140		85/55/140	
Longitudinal		Mean	S.D.	Mean	[illegible]
Raw total quotients	Boys	113.0	19.0	113.7	[illegible]
	Girls	117.6	13.6	115.5	[illegible]
	Total	114.8	17.2	114.4	[illegible]
	n B/G/T	110/83/193		113/84/197	
Cross-sectional (= total)					
Raw total quotients	Boys	113.1	18.7	113.7	[illegible]
	Girls	117.1	14.0	115.3	[illegible]
	Total	114.8	16.9	114.4	[illegible]
Motor	Boys	117.[illegible]	[illegible]	116.3	[illegible]
	Girls	124.2	23.3	117.[illegible]	[illegible]
	Total	1[illegible]0.2	29.2	116.6	[illegible]
Coordination	Boys	104.7	2[illegible].0	107.9	[illegible]
	Girls	107.4	16.7	110.5	[illegible]
	Total	105.9	19.9	109.0	[illegible]
Language	Boys	101.2}	36.1	111.1	[illegible]
	Girls	113.3}	30.5	114.2	[illegible]
	Total	106.4	34.2	112.4	[illegible]
Personal-social	Boys	1[illegible]0.1	[illegible]5.6	116.8	[illegible]
	Girls	1[illegible]1.9	21.1	119.3	[illegible]
	Total	1[illegible]0.9	[illegible]3.7	117.9	[illegible]
Scaled total quotients	Boys	93.4	17.7	99.1	[illegible]
	Girls	102.[illegible]	13.3	101.1	[illegible]
	Total	100.00	16.0	99.9	[illegible]

boys and girls of total and subquotients in the longitudinal and cross-sectional (=total) samples from 3 months to 5 years

levels in this and the following tables * = .05; ** = .01; *** = .001

Brunet-Lézine								Terman-Merrill			
6 mos		12 mos		18 mos		2 yrs		3 yrs		5 yrs	
55/55/140		85/55/140		85/55/140		85/55/140		85/55/140		85/55/140	
Mean	s.D	Mean	s.D	Mean	D	Mean	D	Mean	s.D	Mean	s.D
104.5	8.8	108.1	11.6	103.8	9.4	96.6 **	9.3	101.5	16.1	109.4	14.2
106.3	9.6	108.2	11.1	106.7	8.1	104.1	8.4	105.3	15.3	111.1	10.7
105.2	8.9	106.9	11.4	104.9	9.0	100.8	9.3	102.8	15.9	110.1	12.9
118/84/202		120/86/206		113/82/195		118/84/202		119/84/203		114/80/194	
104.5	9.5	105.7	11.8	103.6	9.3	98.6 ***	8.9	102.1	16.7	110.5	14.8
106.0	9.4	107.2	10.6	107.4	9.0	103.6	9.6	106.5	17.2	111.5	13.6
105.1	[illegible]	106.4	11.5	105.2	9.4	100.7	9.5	103.9	17.0	110.9	[illegible]
107.4	17.1	108.2	21.6	111.0	17.5	104.7	16.1				
107.9	12.4	108.3	18.3	114.0	13.9	109.3	11.3				
107.2	14.6	108.3	20.3	112.5	15.9	106.6	13.8				
101.7	12.0	104.4	18.8	104.0	21.3	96.1	14.9				
103.2	10.8	108.0	12.9	107.2	13.9	99.7	9.8				
102.3	11.6	106.1	16.4	105.3	18.6	97.6	12.1				
106.5 *	23.0	108.0 *	17.7	98.8 **	15.3	96.0 **	16.8				
113.0	22.2	116.4	16.7	104.9	14.7	103.2	14.0				
109.2	22.6	111.8	16.6	99.7	15.7	99.0	16.1				
105.0	12.6	102.8	14.4	99.2	11.8	93.3 ***	13.7				
106.4	12.1	105.9	13.0	102.6	12.1	104.8	16.1				
106.4	12.4	103.9	12.9	100.5	12.2	96.1	15.4				
98.1	15.9	98.1	16.2	97.2 *	16.0	96.4 ***	16.1	98.0	15.8	99.6	[illegible]
101.6	15.9	101.4	15.0	103.0	15.2	104.9	14.1	102.5	16.2	100.6	14.7
100.1	16.9	100.0	16.0	99.9	16.9	100.0	16.0	99.5	16.1	100.6	[illegible]

there are no test items for 27 months; the next step is from now on 6 months instead of 3. Further if a 2-year-old happens to solve an item on the 3-year level, this is not counted in the subscales, which finish at 2½ years.

Regarding individual items, it cannot be expected that all will be given an optimal suitability in character and age level, especially when the test is worked out for another country. For clinical use in Swe-

TABLE 2b. *Sex differences in Griffiths social classes from 18 months to 3 years.*

Class		18 mos Mean	n	2 years Mean	n	3 yrs Mean	n
I+II	Boys	102.2	[illegible]	100.0	31	105.1	[illegible]
	Girls	110.6	16	110.4	20	111.4	[illegible]
III	Boys	96.4	36	97.7	45	96.8	[illegible]
	Girls	100.8	[illegible]	101.1	26	102.2	[illegible]
IV+V	Boys	94.0 *	45	92.8	42 *	93.3	[illegible]
	Girls	102.2	39	104.7	38	97.9	[illegible]

TABLE 3 *Correlation of DQs and IQs between different ages Total sample (T) and strictly longitudinal sample (L)*

The number of children in the different correlations varies between 179 and 190 in the total sampl In the strict longitudinal sample th number is 140, 85 boys, 65 girls.

Parentheses signify correlations which not differ significantly from 0

		Brunet Lézin										Terman Merrill			
		6 mos		9 mos		12 mos		18 mos		2 yrs		3 yrs		5 yrs	
Age ...		T	L	T	L	T	L	T	L	T	L	T	L	T	L
Boys	3 mos	.57	57	48	42	43	43	19	(21)	(18)	(18)	(– 00)	(– 04)	(– 06)	(– 17)
	6 mos			73	72	63	64	.38	42	.34	.29	(– 02)	(– 09)	(– 09)	(– 17)
	9 mos					74	74	48	47	46	40	(06)	(02)	(00)	(– 06)
	[illegible] mos							.54	.50	47	47	(06)	(01)	(03)	(– 04)
	18 mos									.67	65	35	.35	.25	(.21)
	2 yrs											.53	58	42	42
	3 yrs													70	66
Girls	3 mos	.53	41	.36	.3	(15)	(18)	.23	(14)	.25	(.25)	(– 10)	(–.23)	(– 07)	(– 15)
	6 mos			65	67	44	49	45	40	.32	(.25)	(11)	(– 02)	(12)	(– 06)
	9 mos					61	63	.53	49	.31	(..2)	(06)	(– 01)	(14)	(03)
	1 mos							47	[illegible]	40	.30	(1)	(04)	(08)	(02)
	18 mos									61	.33	45	.32	.30	(18)
	2 yrs											48	(.26)	.22	(05)
	3 yrs													.51	55
Total	3 mos	.54	.51	[illegible]	.39	.34	.36	.22	.21	22	.22	(– 02)	(– 08)	(– 04)	(– 16)
	6 mos			60	70	.56	.50	42	[illegible]	34	.29	(05)	(– 05)	(00)	(– 13)
	9 mos					60	70	.50	[illegible]	40	.34	(09)	(02)	(05)	(– 02)
	12 mos							.5	49	44	[illegible]	(12)	(03)	(05)	(– 01)
	18 mos									66	[illegible]	40	.35	.27	.21
	2 yrs											[illegible]	48	37	.31
	3 yrs													63	62

den the Brunet-Lézine test would gain by revision in some respects to make it more adapted to Swedish children.

The Terman-Merrill test has been adapted to Swedish children of preschool ages 1942 by Hellström [13] and by D Katz 1950 [20]. Hellström has translated the whole scale. Her adaptation is the one most commonly used in Sweden and has also been used by us. Her sample was almost exclusively recruited from day nurseries and nursery schools in Stockholm She has not aimed at a representative sampling She has only about 30 children at e.g 3 and 5 years. Katz also found it difficult to obtain a sample representative of the whole country He reports mainly values from a Stockholm sample, which is of greatest interest as a comparison with our results. He has 81 and 89 children at 3 and 5 years of age.

Our mean quotients at 3 and 5 years are higher than the 97 and 100 reported by Hellström.

The corresponding values of Katz are 102 and 108 and thus more similar to ours (104 and 111)

Hellström gives no S.D.s for separate ages. Our S.D.s at 3 and 5 years (17.0 and 13.7) are in good agreement with those of Katz (3 years 16.6 and 5 years 12.2).

Our results, which are based on a sample which is considerably bigger than Hellström's and which appears to have good representativeness for Stockholm, make it probable that her values are too low for contemporary Stockholm children of preschool age.

Correlation Between Different Ages

Results

In order to analyse how constant a child's quotient is from one age to another Pearson correlation coefficients were calculated for boys and girls in both the total sample and the strictly longitudinal sample. The obtained results are shown in Table 3

The differences between the samples are small, with a slight tendency towards somewhat higher values in the total sample The correlations for the girls are often lower than for the boys, especially in the strictly longitudinal sample, where the boys correlations are significantly more often higher than are those of the girls according to the sign test (at the 0.05 level) In this sample the correlations of the girls are especially low between * × 3 years and 2 × 5 years.

Discussion

Our correlations are similar to those found by most other investigators. Table 4 summarizes the correlations between different ages reported by some other investigators (without considering whether the samples are comparable from all points of view) Most authors agree that infant tests are of very little long-term predictive value The correlations between the closest age groups are generally substantial but decrease rapidly with increasing age intervals. As the children grow older the correlation coefficients between test values are higher

Like most others, we can thus state that as regards *normal* children we cannot predict from the 3-12 month values anything about 3-year or 5-year values. Bayley [2], when discussing the low predictive value

TABLE 3 *Correlation of DQs and IQs between different ages Total sample (T) and strictly longitudinal sample (L)*

The number f children in the different correlations varies between 1[illegible] and 180 in the total sample In the strict longitudinal sample the num ber is 140 85 boys, 55 girls.
Parentheses signify correlations which not differ significantly from 0

Age		Brunet-Lézine										Terman Merrill			
		6 mos		9 mos		12 mos		18 mos		2 yrs		3 yrs		5 yrs	
		T	L	T	L	T	L	T	L	T	L	T	L	T	L
Boys	3 mos	.57	.57	45	42	43	43	19	(.21)	(18)	(18)	(– 00)	(– 04)	(– 06)	(– 17)
	6 mos			72	72	63	64	.38	42	.34	.29	(– 02)	(– 09)	(– 09)	(– 17)
	9 mos					74	74	48	47	45	40	(08)	(02)	(00)	(– 06)
	12 mos							54	.50	47	47	(06)	(01)	(03)	(– 04)
	18 mos									07	65	35	35	.25	(21)
	2 yrs											53	.58	42	42
	3 yrs													70	66
Girls	3 mos	.53	41	.36	.32	(15)	(18)	23	(14)	25	(25)	(– 10)	(– 23)	(– 02)	(– 15)
	6 mos			65	67	44	49	45	40	.3	(.25)	(11)	(– 02)	(12)	(– 06)
	9 mos					61	63	53	49	.31	(.22)	(06)	(– 01)	(14)	(03)
	12 mos							47	46	40	.30	(.21)	(01)	(08)	(02)
	18 mos									61	.53	45	.32	.30	(18)
	yrs											48	(.26)	.32	(05)
	3 yrs													.51	55
Total	3 mos	54	.51	42	.39	.34	.36	.23	.21	[illegible]	.23	(– 02)	(– 08)	(– 04)	(– 16)
	6 mos			69	70	.56	.59	42	42	.34	.20	(05)	(– 05)	(00)	(– 13)
	9 mos					69	70	50	[illegible]	40	.34	(09)	(02)	(05)	(– 0*)
	12 mos							.52	49	44	4	(12)	(03)	(05)	(– 01)
	18 mos									66	62	40	.25	.27	..1
	yrs											.53	48	.37	31
	3 yrs													[illegible]	6

den the Brunet Lézine test would gain by revision in some respects to make it more adapted to Swedish children.

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Our mean quotients at 3 and 5 years are higher than the 97 and 100 reported by Hellström.

The corresponding values of Katz are 102 and 108 and thus more similar to ours (104 and 111).

Hellström gives no S.D. for separate ages. Our S.D.s at 3 and 5 years (1[illegible] [illegible] and 13.7) are in good agreement with those of Katz (3 years 16.[illegible] and 5 years 13.3).

Our results, which are based on a sample [w]hich is considerably bigger than Hellström['s] and which appears to have a good representativeness for Stockholm, make it probable that her values are too low for contemporary Stockholm children of preschool age.

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Results

In order to analyse how constant a child's quotient is from one age [illegible] Pearson correlation coefficients were calculated for boys and girls in [illegible] the [illegible] sample and the strictly longitudinal [illegible]. The obtained results are shown in [illegible]

The differences between the samples are small, with a slight tendency towards somewhat higher values in the [illegible]. The correlations for the girls are [illegible] lower than for the boys [illegible] in the strictly longitudinal [illegible] [illegible] the boys correlations are [illegible] often higher than [illegible] according to the [illegible] level). In the [illegible] girls are especially [illegible] and [illegible] years.

Discussion

Our correlations are [illegible] found by [illegible] [illegible]

Like [illegible]

TABLE I Correlations of DQs and [illegible]

	6 mos	9 mos	12 mos	18 mos	2 yrs	3 yrs	5 yrs
3 mos	.57[a] .53(n = 51)[d] .39(n = 141)[g]	42[a] 41(n = 141)[g]	.28[a] 13(n = 29)[d] 42(n = 141)[g]	46(n = 51)[d] 31(n = 141)[g]	− 04 31(n = 141)[g]	− 09[a]	
6 mos		72[a] .59[c] 68(n = 141)[g]	.53[a] .38(n = 191)[b] [illegible] .34(n = 29)[d] 56(n = 141)[g]	11(n = 136)[b] 45[c] .50(n = 108)[d] 62(n = [illegible])[f] 49(n = 141)[g]	23[a] 08(n = 103)[b] .38[c] .37(n = 48)[f] 33(n = 141)[g]	10[a] 23(n = 57)[b] 40(n = 80)[d] 46(n = 31)[f]	21(n = 34)[b] .32(n = 80)[d]
9 mos			.81 69[c] .59(n = 141)[g]	57[c] .56(n = 141)[g]	.30[a] 43[c] 43(n = 141)[g]	22[a]	
12 mos				40(n = 138)[b] .58[c] .53(n = 29)[d] .56[f] 65(n = 141)[g]	60[a] 11(n = 104)[b] .54 53(n = 141)[g]	45[a] 43(n = 58)[b] .33(n = 45)[f]	37(n = 34)[b]
18 mos					52(n = 100)[b] 64[c] 62[f] 07(n = 141)[g]	50(n = 62)[b] .54(n = 80)[d] 15[f]	10(n = 34)[b] 40(n = 80)[d]
2 yrs						76[a] 60(n = 61)[b] 69[c] 66(n = 29)[f]	.58[a] 24(n = 34)[b] 3[illegible]
3 yrs							06[a] .57(n = 34)[b] 78(n = 80)[d] 72[h]

Bayley uses average scores for 1 2, 3; 4 5 6; 7 8, 9; 10, 11 12; 18 21 [illegible]; and 27 30, 36 months. The figures in our table are shown for the last month within each group. The correlations from 2 years to 3 and 5 years and from 3 to 5 years apply not to mean scores for several ages but only to the particular ages.

Bayley [2]: Calif First Year and Calif Preschool

[b] Cavanaugh et al [6]: Cattell and Terman Merrill

Fillioxat-Cowon [7]: Brunet-Lézine

[d] Hindley et al. [14], [15] Griffiths and Terman Merrill

Honzik et al [16]: Calif Preschool

[f] Nelson & Richards [23 24]: Gesell and Stanford Binet.

Sand and Emery Hauzeu [25]: Brunet-Lézine

Sontag et al. [26]: Binet.

of infant tests, summarizes the explanations for this by saying that "scores could be altered by emotional climate, cultural milieu and environmental deprivation on the one hand and by developmental changes in the nature and composition of the behaviours tested on the other"

Developmental Level in Relation to Gestational Age, Sex, Socio-Economic and Family Factors

The developmental level of the children at different ages has been related to the following factors. the gestational age at birth, sex, total social groupings as well as special socio-economic factors and family data such as mother's age, her gainful employment, child's birth order and the time for conception of the child.

Group differences have been compared and tested by χ^2 and t-test.

Relation to Gestational Age at Birth

In tested developmental level during the period close to the birth the gestational age may play a role, greater the closer the test is to the birth.

We have therefore related the length of pregnancy to the DQ values at 3 6 9 and 12 months.

The following four groups were compared by χ^2 analysis:

Gestational age at birth 41 weeks, DQ above the mean	Gestational age at birth 41 weeks, DQ above the mean
Gestational age at birth > 41 weeks, DQ below the mean	Gestational age at birth 41 weeks, DQ below the mean

Result

	χ^2	P
at 3 months	11 13	.001
6	5.51	.02
9	6 44	.01
12	0 72	–

The marked relation between long period of pregnancy and high DQ at 3 month decreases at 6 and 9 months and disappears fully at one year

Discussion

Our results point in the same direction as Cavanaugh's *et al.* although the groups are not divided in quite the same way [6] Comparing IQs of premature mature and postmature infants at 6 12 18 and 36 months, they found at 6 months the means for the postmature group significantly higher than for the mature (0 05 level) At 12 months of age the means for the two groups were identical and thereafter there were no significant differences.

The children may obviously differ greatly in development at an early age, owing to the differences in length of pregnancies. This may contribute to the high standard deviation at 3 months.

Relation to Sex

Results

As will be seen from Table 2a significant differences between the sexes in favour of the girls exist at 18 months 2 years and 3 years with significances at the 0.01 0 001 and 0 05 level respectively (scaled quotients) The difference is greatest at 2 years with an average difference of 8½ points.

We have investigated whether during the years when they are found, the sex differences are evident in all social classes. As seen in Table b this is not so In Graffar intermediate social class (*III*) there are no significant sex differences from 18 months to 3 years, while they are most pronounced in Graffar lowest social class (IV + V) (0 05 level at 18 months and 0 001 at

TABLE 4 *Correlations of DQs and IQs between different ages in some other studies*

	6 mos	9 mos	12 mos	15 mos	2 yrs	3 yrs	5 yrs
3 mos	.57[a] .53(n = 51)[d] .39(n = 141)[g]	4[a] 41(n = 141)[g]	.8[a] 13(n = ?0)[d] 4.(n = 141)[g]	46(n = 51)[d] .31(n = 141)[g]	− .04[a] .31(n = 141)[g]	− .09[a]	
6 mos		72[a] .59[e] 68(n = 141)[g]	52[a] 38(n = 191)[b] 51 .34(n = 20)[d] .56(n = 141)[g]	11(n = 136)[b] 46[e] .56(n = 108)[d] 62(n = ?0)[f] 49(n = 141)[g]	.22[a] 06(n = 103)[b] .38[e] .37(n = 48)[f] .33(n = 141)[g]	10[a] .23(n = 57)[b] 40(n = 80)[d] 46(n = 31)[f]	−.1(n = 34)[b] 3.(n = 80)[d]
9 mos			[illegible] 69[e] .59(n = 141)[g]	.57[e] 56(n = 141)[g]	.39[a] 43[e] 43(n = 141)[g]	.22[a]	
12 mos				40(n = 138)[b] .58[e] .53(n = 20)[d] .56[f] 65(n = 141)[g]	60[a] 11(n = 104)[b] .54 .53(n = 141)[g]	45[a] 43(n = 68)[b] .33(n = 45)[f]	37(n = 34)[b]
18 mos					5.(n = 100)[b] 64[e] 62[f] 67(n = 141)[g]	50(n = 6)[b] .54(n = 80)[d] 15[f]	19(n = 34)[b] 40(n = 80)[d]
yrs						76[a] 50(n = 81)[b] 69[e] 66(n = 29)[f]	.58[a] .24(n = 34)[b] .32[e]
3 yrs							66[a] .57(n = 34)[b] 78(n = 80)[d] 7[a]

Bayley uses verage scores for 1 .., 3, 4 5 6; 7 8, 9- 10 11 12; 18, 1 4; and ?7 30, 36 months. The figures in our table are shown f the last month within each group The correlations from 2 years t 3 and 5 years and from 3 to 5 years apply not to mean scores for several ages but only to the particular ages.

Pilliozat-Cosson [7]; Brunet-Lézine
[d] Hindley *et al.* [14], [15]; Griffiths and Terman M rrill.
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of infant tests summarizes the explanations for this by saying that "scores could be altered by emotional climate cultural milieu and environmental deprivation on the one hand and by developmental changes in the nature and composition of the behaviours tested on the other"

Developmental Level in Relation to Gestational Age, Sex, Socio-Economic and Family Factors

The developmental level of the children at different ages has been related to the following factors: the gestational age at birth, sex, total social groupings as well as special socio-economic factors and family data such as mother's age, her gainful employment, child's birth order and the time for conception of the child

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The following four groups were compared by χ^2 analysis:

Gestational age at birth ≥ 41 weeks, DQ above the mean	Gestational age at birth < 41 weeks, DQ above the mean
Gestational age at birth ≥ 41 weeks, DQ below the mean	Gestational age at birth < 41 weeks, DQ below the mean

Results

	χ^2	p
at 3 months	11 12	.001
6	5 84	.02
9	6 44	01
12	0 72	—

The marked relation between long period of pregnancy and high DQ at 3 month decreases at 6 and 9 months and disappears fully at one year

Discussion

Our results point in the same direction as Cavanaugh *et al.* although the groups are not divided in quite the same way [6]. Comparing IQs of premature mature and postmature infants at 6 12 18 and 36 months, they found at 6 months the means for the postmature group significantly higher than for the mature (0 05 level) At 12 months of age the means for the two groups were identical and thereafter there were no significant differences.

The children may obviously differ greatly in development at an early age owing to the differences in length of pregnancies This may contribute to the high standard deviation at 3 months.

Relation to Sex

Results

As will be seen from Table 2 *a*, significant differences between the sexes in favour of the girls exist at 18 months, 2 years and 3 years with significances at the 0.01 0 001 and 0.05 level respectively (scaled quotients) The difference is greatest at 2 years with an average difference of 8½ points.

We have investigated whether during the years when they are found, the sex differences are evident in all social classes. As seen in Table 2 *b* this is not so In Graffar intermediate social class (III) there are no significant sex differences from 18 months to 3 years, while they are most pronounced in Graffar lowest social class (IV + V) (0.05 level at 18 months and 0.001 at

TABLE 5 *Test items (Brunet Lézine) with significant differences between the sexes*

Subscale	Age of child (months)	Age level of item (months)	Items	Frequency of solution, % Boys	Girls	Total	Significance level boys/girls
Motor	6	6	(P 7) Can sit awhile supported	87.5	97 7	91 9	01
	9	9	(P 2) Can remove a handkerchief placed on the head, sitting unsupported	8 8	96.4	88.4	005
Coordination	9	9	(C 4) Grasps a pell t between thumb and forefinger	56 0	75 9	64.8	01
	12	18	(C 4) Dumps the pellet immediatedly out of the bottle	10 8	1 3	6.8	01
	24	24	(C 3) Tries to fold a piece of paper once	41.5	69 1	53.0	001
Language	3	3	(L 8) Vocalisation prolonged	58 2	77 1	68.3	01
	12	15	(L 8) Says 5 words	30.2	61 6	48.5	005
	12	21	(L 9) Asks for drink and food	0 0	7 0	2.0	005
	18	21	(L 6) Combines 2 words	28.3	51.2	38 0	005
	18	[illegible]	(L 9) Asks for drink and food	[illegible]	48.8	37 4	01
	18	24	(L 6) Names 2 or identifies 4 pictures	8 0	22.0	13.9	01
	18	[illegible]	(L 9) Names itself by Christian name	3.5	15 9	8 7	005
	4	24	(L 8) Says sentences of several words	53 4	75.0	62.4	005
	4	[illegible]	(L 9) Names itself by Christian name	52.5	76.2	62.4	001
Personal Social	18	18	(S 10) Asks for the pot	8.9	23.2	14.9	.01
	18	30	(S 9) Puts on shoes	1.8	19.5	9 2	001
	[illegible]	18	(S 10) Asks for the pot	53 4	79 8	64 4	.001
	4	30	(S 9) Puts on shoes	38 1	77 4	54.5	001

• years of age) In the highest social class (I+II) there is a tendency in the same direction at the same ages (0 10 level)

The differences between the sexes are especially apparent in the *language* and *personal-social* scales, as will be seen in Table 6 As regards language ability significant differences exist at all ages except 6 months. The girls lead is most marked from 12 4 months of age Since some uncertainty attaches to the 3-month language item and the language items t proximate age levels (.. and 4 months) show no significant difference between the sexes, we do not attach importance to the significant sex difference at 3 months of age.

As regards the personal-social sphere it should be pointed out that, during the period when the girls lead is most marked, this is in the dressing and toilet-training items. The item in which girls are definitely most dvanced is putting on shoes

Another "social" item with highly significant sex difference is asking for the pot

Table 6 shows the differences between the sexes for all items in the Brunet-Lézine test that are significant at least on the 0 01 le el.

As is known, the Terman-Merrill test, which was used for measuring the development t 3 and 5 years of age is not divided into subscales. But we can elucidate some spects of the subsequent language development t 3 and 5 years through two sources 1) language items in the Terman-Merrill test and) ratings of language development by the psychologist

A regards the *Terman Merrill language items* we chose for *3-yea -old* the picture vocabulary item as it is most closely equivalent to one of the language items at 2 years.

We divided the children into two groups: 1) those who could name at least 14 pictures, and 2) those who could name at most 13 pictures According to a χ^2 test there was no significant difference between the sexes (see Table 6)

For the *5-year-old* we chose the Terman-Merrill vocabulary test" as a measure of language development. The children were divided into two groups: 1) those who could define" at least 5 words and 2) those who could define at most 4 words.

Nor did the χ^2 test show any significant difference between the sexes at 5 years of age (see Table 6)

Five-point scales were used for the *psychological rating* of the children s speech development, 1 denoting lowest and 5 highest degree The language aspects assessed at 3 and 5 years of age were: 1) enunciation, 2) maturity of language use (length and complexity of sentence formation and vocabulary in use) and 3) comprehension of language. (For detailed definition of the 5 points of the scales see appendix 1)

At 3 years of age but not at 5 the χ^2 test shows significant differences in favour of girls in all three areas, at the 0 01 level for enunciation and comprehension of language; at the 0 05 level for maturity of language use (see Table 6)

Discussion

Some authors have found significant sex differences during the preschool years, others have not.

From the parallel studies significant sex differences have been reported by H Fischer [8] In the Zürich study most

TABLE 5 *Test items (Brunet-Lézine) with significant differences between the sexes*

Subscal	Age of child (months)	Age level of item (months)	Items	Frequency of solution, % Boys	Girls	Total	Significance level boys/girls
Motor	6	6	(P 7) Can sit awhile supported	87.5	97 7	91 9	01
	9	9	(P 2) Can remove a handkerchief placed on the head sitting unsupported	82.6	96 4	88 4	005
Coordination	9	9	(C 4) Grasps a pellet between thumb and forefinger	56 9	75 9	64.8	01
	12	[illegible]	(C 4) Dumps the pellet immediatedly out f the bottle	10.8	1 2	6 8	01
	24	24	(C 3) Tries to fold a piece of paper once	41.5	69 1	53 0	001
Language	3	3	(L 8) Vocalisation prolonged	56.2	77 1	66.3	01
	[illegible]	15	(L 8) Says 5 words	30 2	61 6	48.5	005
	12	21	(L 9) Asks for drink and food	0 0	7 0	2.9	005
	18	21	(L 8) Combines 2 words	28 3	51.3	38 0	005
	18	[illegible]	(L 9) Asks for drink and food	29.2	48 8	37 4	01
	18	[illegible]	(L 6) Names 2 or identifies 4 pictures	8 0	22 0	13.9	01
	18	24	(L 0) Names itself by Christian name	3.5	15 9	8 7	005
	4	[illegible]	(L 8) Says sentences of several words	53 4	75 0	62 4	005
	[illegible]	[illegible]	(L 0) Names itself by Christian name	52.5	76.3	62.4	001
Personal Social	18	18	(S 10) Asks for the pot	6.9	23 2	14 9	01
	18	[illegible]	(S 9) Puts on shoes	1 6	19 5	[illegible]	001
	[illegible]	[illegible]	(S 10) Asks for the pot	53 4	79 8	64.4	001
	24	30	(S 9) P ts on hoes	38 1	77 4	54.5	001

marked at 18 and 24 months in favour of girls. From the Brussels study [27] however E. A. Sand and C. Emery Hauzeur report no difference although they used the same test (Brunet-Lézine)

In the London study where the Griffiths test was used, a slight, though not significant, tendency to higher mean scores was found for girls at 18 months [14] (at 3 years of age the London children were not tested by Griffiths test)

In the second sample of the Fels study [28] the same tendency was noticeable as in our study the sex difference being greater at and 3 years of age than at 5 years.

N Bayley found no differences in her Berkeley study

These diverging results may be due to differences between countries but are more probably associated with other factors

A factor which may be of significance is the composition of the various samples In our study the sex differences do not appear to be evenly distributed over the social classes but occur mainly within the lowest class. If this applies also to other studies, it may explain that sample where the lowest social class is not represented in due proportion does not show any sex difference

Another factor may be the use of different test items, some of which are more sex-differentiating than others

Many of the items in Bayley s mental scale for example most closely resemble those in Brunet Lézine s coordination scale where in our material no significant sex differences are found either Bayley s scale on the other hand, does not comprise the most sex-differentiating items used by us, e.g those concerning dressing and toilet training Nor does it include our most sex-differentiating language items: to name oneself by Christian name.

The girls lead in language development t an early stage has been confirmed by many authors. McCarthy reports fourteen major studies of the average length of sentences at ages of the 18 months to 9½ years. Of the 64 comparisons between boys and girls, 43 are in the girls favour and only 18 is in the favour of th boys.

If one considers the seven studies reported by McCarthy from 18 months to 3 years of age, one finds that, of the 23 comparisons made, almost all, 21 are in the girls' favour and only one is in the favour of the boys. According to McCarthy sampling errors were involved here in that the girls of that age group came in undue proportion from the lower socio-economic levels [22] In McCarthy s study of the language development of the preschool child (ages 18–54 months) she reports the greatest sex differences as percentage comprehensible responses at the ages 18 and 24 months. The girls gave 38 % and 78 % comprehensible answers at 18 and 24 months respectively and the boys 14 % and 49 % [23] Young [31] found language differences between the sexes to be more pronounced in children of lower socio-economic status. This points in the same direction as our finding of developmental level as a whole.

As regards dressing behaviour Gesell [10] reports a marked sex difference

Summarizing the results as regards sex differences up to 5 years, no significant differences are generally found during early infancy During the next 2 years there is evidence of a more rapid develop-

TABLE 6 *Language development at 3 and 5 years*

Terman–Merrill		Sex: Boys		Sex: Girls		Graffar social classes: I + II		III		IV + V		Mother educ level: High (1–3)	Low (4 5)
Picture vocabulary (3 yrs)		n		n		n		n		n		n	n
Can name at least 14 pictures		57		43		35		[illegible]		33		40	60
Can name at most 13 pictures		[illegible]		41		20		36		47		22	80
		$\chi^2=0.21$ $df=1$ n. sig				$\chi^2=6\ 74$ $df=$ .., 05						$\chi^2=8\ 06$, $df=1$ 01	
Vocabulary (5 yrs)													
Can define at least 5 words		62		40		42		38		22		42	50
Can define at most 4 words		53		30		17		41		34		18	84
		$\chi^2=0.20$ $df=1$ n. sig				$\chi^2=1..79$ $df=2$ 005						$\chi^2=17\ 76$, $df=1$ 001	
Ratings		3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs	3 yrs	5 yrs		
Enunciation	Low (1–3)	88	[illegible]	49	[illegible]	[illegible]	11	48	24	57	[illegible]		
	High (4–5)	[illegible]	73	36	58	24	40	18	55	[illegible]	97		
		3 yrs. $\chi^2=6\ 08$, $df=1$ 01 5 yrs: $\chi^2=1.36$, $df=1$ n. sig				3 yrs: $\chi^2=4\ 36$ $df=$ .., n. sig. 5 yrs: $\chi^2=15\ 06$ $df=2$ 001							
Maturity of language use	Low (1–3)	96	70	57	50	35	[illegible]	50	51	68	45		
	High (4–5)	1	48	28	30	21	36	16	28	[illegible]	11		
		3 yrs: $\chi^2=5.24$ $df=1$ 05 5 yrs: $\chi^2=0\ 01$ $df=1$ n. sig				3 yrs: $\chi^2=9\ 08$ $df=2$, .20 5 yrs: χ $=20\ 44$ $df=2$, 001							
Comprehension of language	Low (1–3)	69	70	[illegible]	44	29	[illegible]	45	48	63	41		
	High (4–5)	[illegible]	45	36	36	26	38	[illegible]	31	17	1		
		3 yrs: $\chi^2=7.2$.., $df=1$ 01 5 yrs: $\chi^2=0\ 45$ $df=1$ n. sig.				3 yrs: $\chi^2=10\ 17$ $df=$ 01 5 yrs: $\chi^2=21\ 23$ $df=2$, 001							

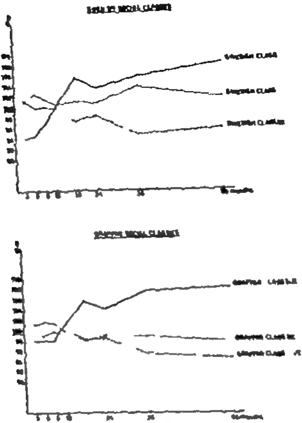


Fig. 1 Mental development in relation to social class.

ment rate for the girls, especially in the language and personal-social spheres. This tendency seems to be most pronounced in the lowest socio-economic class. Later there is a period of less pronounced differences indicating catch-up of the boys.

Relation to Socio-Economic Factors

The socio-economic background of each child was evaluated by means of two different systems: one Swedish, 3-grouped scale and one 5-point scale according to Graffar. The latter is based on five different partial factors (for further details see paper II of our series).

The overall social groupings (Graffar and Swedish social classes) as well as the special factors of housing standard, assessed income, occupation and mother's educational level were related to the scaled total quotients from 3 months to 5 years and to subscale quotients of the Brunet Lézine from 3–4 months.

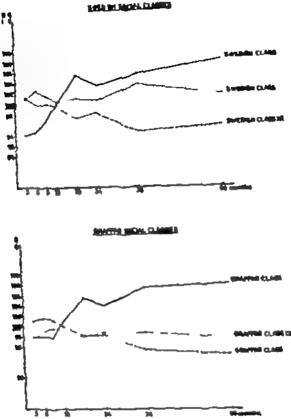
The differences in mean quotients were tested by the *t*-test.

Results

Developmental level and overall social groupings. Table 7 and Fig. 1 show the *total scaled quotients* for children classified

TABLE 7 *Means of scaled total quotients by social class according to Swedish and Graffar system from 3 months to 5 years and mean subscale raw quotients by social class according to Graffar from 3–24 months*

Classes	Age		Brunet-Lézine 3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	Terman Merrill 3 yrs	5 yrs
Swedish:	n. I/II/III		28/72/93	32/74/93	31/74/97	35/76/95	31/72/93	31/83/88	31/82/90	31/82/81
I, II III	Total	I	94	95	97	100	106	103	106	106
	scaled	II	101	102	103	100	101	101	104	101
	DQ, IQ	III	101	100	100	100	97	98	95	96
Graffar: I + II, III IV + V	n. I + II/III/IV + V		45/59/89	49/63/87	48/61/93	52/63/92	48/60/87	51/71/80	56/67/80	59/70/58
	Total	I + II	98	98	98	101	106	104	108	108
	scaled	III	100	99	100	99	96	99	99	98
	DQ, IQ	IV + V	101	103	101	100	98	96	96	95
Graffar	Motor	I + II	116	118	107	105	116	108		
		III	123	115	108	106	111	108		
		IV + V	124	119	108	109	112	106		
	Coordination	I + II	105	106	102	108	112	102		
		III	107	109	103	105	107	97		
		IV + V	107	111	105	105	104	98		
	Language	I + II	113	111	107	113	103	101		
		III	103	113	108	111	99	100		
		IV + V	107	114	112	111	100	98		
	Social	I + II	121	117	104	105	102	98		
		III	122	118	105	104	100	98		
		IV + V	123	119	100	103	100	99		



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Classes	Age		Brunet-Lézine						Terman Merrill	
			3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	3 yrs	5 yrs
Swedish	n. I/II/III		28/72/93	32/74/93	31/74/97	35/76/95	31/72/92	31/83/88	31/82/90	31/82/81
	Total	I	94	95	97	100	106	103	106	108
I, II, III	scaled	II	101	102	102	100	101	101	104	101
	DQ IQ	III	101	100	100	100	97	98	95	96
Graffar	n. I+II/III/IV+V		45/59/89	49/63/87	48/61/93	52/62/92	48/60/87	51/71/80	56/67/80	50/70/56
I+II III	Total	I+II	98	98	98	101	106	104	108	108
IV+V	scaled	III	100	99	100	99	98	90	90	98
	DQ IQ	IV+V	101	102	101	100	98	98	96	95
Graffar	Motor	I+II	116	118	107	106	116	108		
		III	123	116	106	106	111	108		
		IV+V	124	119	108	109	112	106		
	Coordination	I+II	105	106	102	108	112	102		
		III	107	109	103	105	107	97		
		IV+V	107	111	102	105	104	98		
	Language	I+II	112	111	107	113	103	101		
		III	103	113	108	111	90	100		
		IV+V	107	114	112	111	100	98		
	Social	I+II	121	117	104	105	102	95		
		III	122	118	105	104	100	98		
		IV+V	123	119	100	103	100	99		

Table 8 (continued)

	Age		Brunet-Lézine						Terman Merrill	
			3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	3 yrs	5 yrs
(Grouped.) High (more than elementary school): 1+2+3 H	Motor	H	116	117	106	106	116	106		
		L	123	118	106	106	112	107		
	Coordi nation	H	103	107	103	106	112	102 *		
		L	107	110	103	105	106	97		
	Language	H	104	109	110	116 (*)	103	104		
		L	106	114	110	110	99	98		
Low (only elementary education): 4+5 L	Personal-social	H	118	116	106	106	101	98		
		L	123	119	107	103	100	98		

according to both Graffar scale and Swedish scale. Since there were few children referable to Graffar extreme classes classes I+II are combined to one as well as IV+V According to Swedish grouping, the children of the highest class have significantly lower DQs than the other two classes at 3 and 6 months. The same tendency although never significant can be seen in Graffar social classes. As from 18 months of age, on the other hand, the children in the highest class re significantly more developed

These class differences from 18 months are not found in all *subscale quotients* of the Brunet-Lézine test but only in the coordination scale (Table 7)

The further relation of language development (at 3 and 5 years) to social grouping were studied by Terman Merrill items and ratings (cf page 011) As seen from Table 6 significant differences were found between social classes both in Terman-Merrill items and in ratings. The children in the highest class are throughout most and the lowest class least developed.

Development level and special socio-economic grouping When studying the relation of the level of mental development to housing standard, income occupation of the family and level of education of the mother we divided the children into a high and a low group for each of these factors. The results are shown in Table 8 It is only the parents income that at 3 and 6 months, is significantly related to the total *DQs* parents with the highest income having the least developed children. A relation in the opposite direction is earliest manifested in respect of mother s educational level and the family s occupational status (from 18 months) At 3 and 5 years, however the children with better conditions in all four socio-economic scales have significantly higher IQs.

The relation of the special socio-economic factors to subquotients from 3 months to years is shown in Table 8. The main results are: At an early age parents in the *low income* group have children with higher *DQs* in the motor (3 months) coordination (3 and 6 months) and personal-social (3 months) spheres.

Significant differences in the opposite

TABLE 8 *Means of scaled total quotients from 3 months to 5 years and means of subscale raw quotients from 3 months to 24 months in relation to Housing standard Income Occupational standard and Mother s educational level*

	Age		Brunet-Lézine						Terman Merrill	
			3 mos	6 mos	9 mos	1 mos	[illegible] mos	yrs	3 yrs	5 yrs
Housing standard	n. H/L		31/162	33/166	31/171	35/171	3*/163	43/159	57/146	83/1[illegible]
(Grouped.) High: 1+2 = H Low: 3+4+5 = L	Total scaled DQ IQ	H	97	97	97	97	10*	10*	107}	10*}
		L	101	101	101	101	100	99	[illegible]}	96}
	Motor	H	114	116	106	104	115	109		
		L	123	118	108	108	11	107		
	Coordination	H	102	105	101	104	106	99		
		L	107	110	103	106	107	99		
	Language	H	110	111	106	110	101	101		
		L	107	113	111	11	100	99		
	Personal social	H	1*0	117	103	10*	103	97		
		L	122	118	107	104	100	98		
Income standard	n H/L		4/166	4/171	4/174	*7/175	*6/167	34/167	53/146	
(Grouped) High: 1+ = H Low: 3+4+5 = L	Total scaled DQ IQ	H	[illegible]}	0*}	95	101	100	104	107}	
		L	10*}	101}	101	100	100	99	98}	
	Motor	H	108}	114	106	108	115	110		
		L	120}	118	108	107	113	107		
	Coordination	H	92}	100}	99	107	106	100		
		L	108}	110}	102	106	107	98		
	Language	H	97	108	105	110	99	103		
		L	109	114	111	11	100	99		
	Personal social	H	108}	114	102	103	101	97		
		L	123}	119	107	104	100	[illegible]		
Occupational standard	n. H/L		51/14	56/142	54/146	59/147	55/140	58/144	62/141	63/13
	Total scaled DQ IQ	H	99	98	99	100	104}	104}	107}	107}
		L	101	101	101	100	98}	98}	97}	[illegible]}
(Grouped) High. 1+ = H Low: 3+4+5 = L	Motor	H	116	117	107	105	115	108		
		L	122	118	108	108	11	107		
	Coordination	H	105	106	102	107	112}	101}		
		L	107	110	103	106	105}	98}		
	Language	H	11	112	108	114	102	10*		
		L	106	112	111	111	100	98		
	Personal social	H	123	116	105	103	101	98		
		L	1 1	119	107	104	100	[illegible]		
Mother s educational level	n H/L		54/139	61/133	61/141	64/14	57/138	61/141	6 /141	60/13
	Total scaled DQ IQ	H	97	97	90	10*	103}	103}	10*}	107}
		L	101	101	100	99	98}	98}	97}	[illegible]}

Table 8 (continued)

			Brunet-Lézine						Terman-Merrill	
	Age		3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	3 yrs	5 yrs
(Grouped) High (more than elementary school): 1+2 3 H	Motor	H	116	117	108	105	116}	108		
		L	123	118	108	108	112}	107		
	Coordination	H	103	107	103	106	113}	103} ***		
		L	107	110	103	105	105}	97}		
	Language	H	106	109	110	118} (*)	103} *	104}		
		L	106	114	110	110}	99}	95}		
Low (only elementary education): 4+5 L	Personal-social	H	118	116	108	105	101	98		
		L	123	119	107	103	100	98		

according to both Graffar scale and Swedish scale. Since there were few children referable to Graffar extreme classes, classes I+II are combined to one, as well as IV+V. According to Swedish grouping the children of the highest class have significantly lower DQs than the other two classes at 3 and 6 months. The same tendency, although never significant, can be seen in Graffar social classes. As from 18 months of age, on the other hand, the children in the highest class are significantly more developed.

These class differences from 18 months are not found in all *subscale quotients* of the Brunet-Lézine test but only in the coordination scale (Table 7).

The further relation of language development (at 3 and 5 years) to social grouping were studied by Terman-Merrill items and ratings (cf. page 011). As seen from Table 6 significant differences were found between social classes both in Terman-Merrill items and in ratings. The children in the highest class are throughout most and the lowest class least developed.

Developmental level and special socio-economic grouping. When studying the relation of the level of mental development to housing standard, income, occupation of the family and level of education of the mother, we divided the children into a high and a low group for each of these factors. The results are shown in Table 8. It is only the parents' income that, at 3 and 6 months, is significantly related to the total *DQs*, parents with the highest income having the least developed children. A relation in the opposite direction is earliest manifested in respect of mother's educational level and the family's occupational status (from 18 months). At 3 and 5 years, however, the children with better conditions in all four socio-economic scales have significantly higher IQs.

The relation of the special socio-economic factors to *subquotients* from 3 months to 5 years is shown in Table 8. The main results are: At an early age parents in the low income group have children with higher DQs in the motor (3 months), coordination (3 and 6 months) and personal-social (3 months) spheres.

Significant differences in the opposite

TABLE 8 *Means of scaled total quotients from 3 months to 5 years and means of subscale raw quotients from 3 months to 24 months in relation to Housing standard Income Occupational standard and Mother's educational level*

	Age		Brunet-Lézine						Terman Mer	
			3 mos	6 mos	9 mos	12 mos	18 mos	yrs	3 yrs	5
Housing standard	n H/L		31/162	33/166	31/171	35/171	3 /163	43/150	57/146	88/
	Total scaled	H	97	97	97	97	103	10*	107}	10
(Grouped.)	DQ IQ	L	101	101	101	101	100	99	97}	9
High: 1+2=H	Motor	H	114	116	106	104	115	109		
Low: 3+4+5=L		L	123	118	108	108	112	107		
	Coordination	H	102	105	101	104	108	99		
		L	107	110	103	106	107	99		
	Language	H	110	111	106	110	101	101		
		L	107	113	111	112	100	99		
	Personal social	H	120	117	103	102	103	97		
		L	122	118	107	104	100	98		
Income standard	n H/L		24/166	24/171	24/174	27/175	26/167	34/167	53/146	
(Grouped.)	Total scaled	H	88} *	93}	95	101	100	104	107}	
High: 1+2=H	DQ IQ	L	102}	101}	101	100	100	99	98}	
Low: 3+4+5=L	Motor	H	108}	114	106	108	115	110		
		L	123}	118	108	107	112	107		
	Coordination	H	92}	100}	99	107	106	100		
		L	108}	110}	103	106	107	98		
	Language	H	97	108	105	110	99	103		
		L	109	114	111	112	100	99		
	Personal social	H	108}	114	102	103	101	97		
		L	123}	119	107	104	100	98		
Occupational standard	n H/L		51/143	66/143	64/148	59/147	65/140	58/144	62/141	63/
	Total scaled	H	99	98	99	100	104}	104}	107}	107
	DQ IQ	L	101	101	101	100	98}	98}	97}	97
(Grouped.)	Moto	H	116	117	107	105	115	108		
High: 1+2=H		L	123	118	108	108	11	107		
Low: 3+4+5=L	Coordination	H	105	106	103	107	11 }	101}		
		L	107	110	103	106	103}	98}		
	Language	H	112	123	108	114	102	102		
		L	106	113	111	111	100	93		
	Personal social	H	1*3	116	105	103	101	98		
		L	1 1	119	107	104	100	98		
Mother educational level	n H/L		54/139	61/138	61/141	64/142	57/138	61/141	6 /141	60/1
	Total scaled	H	97	97	99	102	106}	105}	109}	107
	DQ IQ	L	101	101	100	99	95}	98}	97}	97}

TABLE 9 *Means of scaled total quotients and mother's employment*

Age	Brunet-Lézine			Terman Merrill	
	1 yr	18 mos	2 yrs	3 yrs	5 yrs
e/h	20/116	28/107	29/115	29/118	47/133
Children of gainfully employed mothers =	100	100	100	104	98
Children of housewives = h	101	102	101	100	101

low socio-economic grouping are more developed at 3 and 6 months of age. It is, however only in one of the partial factors the income, that this difference is significant. Possibly this could depend upon the fact that the high income group (1+2) is the altogether smallest group It amounts only to 13 % of the entire sample (at 1 year) as against, for instance 28 % for the high occupational group. But even if we cut off a similar small percentage of occupational and educational scales, we still do not get significant differences at 3 and 6 months in these two partial scales.

Relation to the Gainful Employment of the Mother

The mother's being at home or not is supposed to be of great significance in the development of the child. We have compared the developmental level of children of gainfully employed mothers and others The first group consisted of mothers employed part time or full-time, when the children were 1 [illegible] and 3 years of age Group 2 consisted of children whose mothers were at home at the same ages. The number of mothers who had continuous employment during the first 5 years of life of their children was too small to constitute a separate group (n=9). At 5 years, therefore, we compared the children of mothers employed and not employed only at this age

Results

As will be seen from Table 9 there is no significant difference in development level between the two groups at any age

Relation to Mother's Age

The maternal age in our sample varies between 15 and 42 years at the birth of the child The situation of the young mother may differ from that of older mothers in many respects. Young mothers have e.g the less satisfactory financial and housing conditions

We divided the children into three groups according to maternal age 1) children of young mothers (<25 years) 2) children of medium-aged mothers (25–32 years), and 3) children of older mothers (>32 years)

Results

Table 10 shows the scaled mean quotients within these groups from 3 months to 5 years of age

As will be seen, there is no significant difference between the groups before the age of 2.

direction are found between the high and the low groups of occupation and mother's educational level. The high group children are more developed in coordination at 18 and 24 months.

Mother's educational level is the only factor related to the language DQ and this already from 12 months ($t = 1.96$ almost 0.05 level). The significance level rises successively to 0.02 at 18 months and 0.01 at 2 years. Also at 3 and 5 years there are significant differences in language development between children of mothers with high and low educational level, most pronounced at 5 years (see Table 6) again in favour of the more educated goup.

Discussion

An increasing relation between development level and socio-economic status during the preschool years has been reported by several workers (e.g. Bayley [2] Hindley [15] Honzik [17] Sand Hauzeur [27]. Some find significant differences as early as 18 months and 2 years of age (Bayley, Sand Hauzeur) others not until 3 years (Hindley, Honzik). Our observations point in the same direction.

The course of this differentiation process is however far from clear.

"Social class" and "total development quotient" are collective terms for different not always closely related factors. By examining the relations between socio-economic special factors and quotients for the subscales in the test one gets a clearer idea of the role and development of different factors, and relations which are otherwise concealed may come to light. The positive relation between social class and developmental level is found as early as 18 months in our material and this depends mainly upon the significantly differentiating partial factors of family occupation and mother's educational level.

A correlation between the parents' level of education and the mental development of children has been reported by several authors.

Van Alstyne [30] in her study from 1929 of 75 children aged 3 years in New York City reports a correlation of 0.60 between the children's intelligence (measured by Kuhlman-Binet's test) and the mother's education, and of 0.51 with father's education.

Nancy Bayley [1] in her study from California found a negative correlation between the parents' educational level and infant development but after 1 year the correlation became positive and between 1 and 2 years increased sharply, the better educated parents having children with higher mental development. In a recent report [3] from a study of American children from 1–15 months, she finds no difference in developmental level on the basis of educational level of either father or mother.

We found no significant difference in language development during the first two years, using social class classification while as early as 1 year there are almost significant differences in language development between children of mothers with different educational level. This relation becomes gradually stronger at 18 months and 2 years. Mother's educational level seems thus to be the most important factor and the children's language the sphere where one can trace this influence earliest. Using only overall social class this early association would have been overlooked. The children from

TABLE 11 *Means of scaled total quotients from 3 months to 5 years by children's birth order of illegitimate and legitimate children of children conceived before and after marriage as well as mean quotients for subscales of first-born and second-born children from 3 to 24 months*

	Age		Brunet-Lézine						Terman-Merrill	
			3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	3 yrs	5 yrs
Children birth order Firstborn = I Second born II Others III	n: I/II/III		78/78/25	81/86/23	81/85/26	82/86/28	78/88/24	80/85/37	82/84/27	78/82/24
	Total scaled DQ, IQ	I	103	104 **	104 *	102	102	104 **	101	98
		II	98	95	97	99	99	97	101	103
		III	101	100	101	101	97	96	97	99
	n, I/II			81/86	81/85			80/85		
	Motor	I		122 ***	110 *			109		
		II		113	106			105		
	Coordination	I		112 **	104			99		
		II		105	101			98		
	Language	I		116 *	114 *			104 *		
		II		106	106			95		
	Personal-social	I		121 **	109			100		
		II		114	104			96		
Illegitimate (I) Legitimate (L) Children	n, I/L		21/172	23/176	23/179	23/183	21/174	22/180	23/181	21/173
		I	98	101	101	96	96	97	95	91 *
		L	100	100	100	100	101	100	100	101
Children conceived before (b), after (a) marriage	n, a/b		61/133	63/136	65/137	66/141	62/133	62/140	64/139	60/134
		b	103	104 **	101	101	97	98	97	95 ***
			99	98	100	100	101	100	101	103

Results

The mean quotients of the three groups are shown in Table 11 First-born compared with second children seem to be more advanced during the first 2 years; at 6 and 9 months and years the difference is significant in relation to second born.

W have also compared the mean quotients for the subscales in Brunet Lézine for the first born and second-born at the ages when there are significant differences in the total quotients.

At 6 months it is particularly in the motor and social spheres that the mean differences in favour of the first-born are greatest, although significant in all spheres. At 9 and 24 months the first-born are still superior in motor development, although less markedly so

In coordination there is a significant difference only at 6 months, while there are significant differences in language development between first- and second born at 6 9 and 4 months. The level of significance decreases in all spheres except in language, where it becomes higher with increasing age

TABLE 10 *Means of scaled total quotients (3 months–5 yrs), and of subquotients (3 months–2 yrs) by mother's age*

Age			Brunet Lézine 3 mos	6 mos	9 mos	[illegible] mos	18 mos	[illegible] yrs	Terman-Merrill 3 yrs	5 yrs
Mother's age (Grouped:) Young: < 25 yrs = Y Medium: 26–32 yrs = M Older: > 32 yrs = O	n. Y/M/O		83/70/31	83/85/31	84/84/34	87/85/34	82/78/35	85/84/33	87/83/33	[illegible]/80/32
	Total scaled DQ IQ	Y	103	101	10[illegible]	101	100	10[illegible]	97	[illegible]
		M	98	99	99	99	101	100	104	103
		O	[illegible]	100	99	99	99	94	[illegible]	97
	Motor	Y	129	1[illegible]1	109	110	113	108		
		M	114	115	108	105	112	106		
		O	119	117	105	105	111	107		
	Coordination	Y	108	108	103	106	105	100		
		M	105	110	102	106	109	98		
		O	106	109	103	106	107	97		
	Language	Y	106	115	112	112	101	101		
		M	113	111	108	111	101	101		
		O	98	115	107	109	[illegible]	92		
	Personal social	Y	121	119	108	105	101	100		
		M	124	117	106	104	100	93		
		O	118	118	105	103	99	95		

At 2 years the means for the children of old mothers are unusually low (93.8); the *difference from that of the children of young mothers is significant.*

At 3 and 5 years there is a significant difference between the children of medium aged and young mothers and likewise between the children of medium-aged and older mothers. In all cases the children of medium-aged mothers have the highest quotients.

The various age groups were also compared with regard to the subquotients from 3 months to 2 years. The results are presented in Table 10.

The children of young compared with medium-aged mothers have a tendency to better motor development, especially at 3 and 6 months when the differences are significant.

As regards language development the children of older mothers are on a very low level at 2 years of age (92.3) when they *differ significantly* from the children both of young and of medium-aged mothers.

Relation to Order of Birth

The order of birth of a child in the family is often considered to be of significance in its development. Is any difference in mental development level noticeable between children with different successional number in the family? What is the effect, for example, of the greater attention and the *perhaps often rather anxious care* devoted to the first-born child?

Our material was divided into three groups—two of roughly equal size, first-born ($n = 84$) and second born ($n = 90$) while third and *subsequent children* ($n = 38$) constitute the third group.

TABLE 11 *Means of scaled total quotients from 3 months to 5 years by children's birth order of illegitimate and legitimate children, of children conceived before and after marriage as well as mean quotients for subscales of first-born and second-born children from 3 to 24 months*

	Age		Brunet-Lézine 3 mos	6 mos	9 mos	12 mos	18 mos	2 yrs	Terman-Merrill 3 yrs	5 yrs
Children birth order	n. I/II/III		78/79/30	81/86/33	81/85/36	82/86/28	76/85/34	80/85/37	83/84/37	78/82/34
Firstborn I	Total	I	102	104 ***	104	102	102	104 **	101	98
Second born II	scaled	II	96	95	97	99	96	[illegible]	101	103
Others III	DQ, IQ	III	101	103 *	101	101	97	96	97	99
	n. I/II			81/86	81/85			80/83		
	Motor	I		122 **	110			109 *		
		II		113	106			103		
	Coordination	I		112 *	104			99		
		II		106	101			95		
	Language	I		115 *	114 *			104 **		
		II		109	106			96		
	Personal-social	I		121 **	109 *			100		
		II		114	104			96		
Illegitimate (I)	I/L		21/173	23/176	23/179	23/163	21/174	22/180	22/181	21/173
Legitimate (L)		I	98	101	101	99	96	97	95	91 **
Children		L	100	100	100	100	101	100	100	101
Children conceived	a/b		61/132	63/136	65/137	65/141	62/133	62/140	64/139	60/134
before (b),		b	102	104 **	101	101	97	99	97	98 ***
after (a) marriage		a	99	98	100	100	101	100	101	103

Results

The mean quotients of the three groups are shown in Table 11. First-born compared with second children seem to be more advanced during the first – years; at 6 and 9 months and years the difference is significant in relation to second born.

We have also compared the mean quotients for the subscales in Brunet Lézine for the first-born and second-born t the ages when there are significant differences in the total quotients.

At 6 months it is particularly in the motor and social spheres that the mean differences in favour of the first-born are greatest, lthough significant in all spheres. At 9 and 24 months the first-born are still superior in motor development al though less markedly so.

In coordination there is a significant difference only at 6 months, while there are significant differences in language development between first- and second born at 6 9 and 24 months. The level of signif icance decreases in all spheres except in language, where it becomes higher with increasing age.

In ratings of language development at 3 and 5 years the only significant difference between first-born and others is in enunciation (0 05 level) at 3 years (see Table 6)

Ratings were also made of the children's vocal communicativeness from 1 to 5 years of age on a 5-point scale 1 representing the lowest and 5 the highest degree of communicativeness. First born and others were compared by χ^2 testing with respect to rated communicativeness. At 2 and 3 years there is a significant difference between first-born and others (0 005 and 0 02 respectively $\chi^2 = 12\ 66$ and $8\ 788$ $df = 2$) Also at 18 months there is a tendency in the same direction (0 10 $\chi^2 = 4.718$ $df = 2$) At these ages the first born are throughout the most communicative At one and five years the differences are not significant ($\chi^2 = 1\ 016$ and $2\ 020$ $df = 2$)

Discussion

The better development found in the first born during the first years is in good agreement with the findings of Bayley [3] She found in American children tested from 1–15 months of age that first born compared with others obtained higher scores at 11 ages (of 15) The results may well be due to the fact that parents give greater attention to their first-born.

One reason why the first born are no longer in the lead after the first years may be that by then they have more often got younger siblings. Up to 5 year of age 55% ($n = 46$) of the first-born had got siblings as against 22% ($n = 28$) of the rest

We have calculated the mean difference between the quotients at 1 and 3 years for children who got or who did not get siblings during their first 3 years of life In the first group the quotients fell by an average of 8.3 points In the group without siblings up to 3 years the quotients rose by an average of 2.3 points. The difference between these mean differences is highly significant ($t = 3\ 49$ 0 001) In the same way the mean differences were calculated from 3–5 years for those who got and those who did not get siblings during that period In the group who did not get siblings between their third and fifth year the IQ went up by an average of 0.36 point in the other group it fell by an average of 1.29 points. The difference between these values is not significant ($t = 0\ 72$)

Relation to Conditions of Conception

Our material includes 23 illegitimate children. We have compared this group with the group of legitimate children.

Results

Table 11 shows that there were no significant differences before the age of 5 years, when the difference is clearly significant in favour of the legitimate children At 18 months and 3 years there is a tendency in the same direction.

We have also compared children conceived before with those conceived after marriage At 6 months the children conceived before marriage were significantly more developed than those conceived after marriage From 18 months the tendency is in the opposite direction and at 5 years the difference is highly significant in favour of the children conceived in wedlock (Table 11)

A comparison between illegitimate children and those conceived before but born

in wedlock shows no significant difference up to 3 years. At 5 years the children conceived before marriage have higher quotients than have illegitimate children, the difference being significant at the 0.01 level.

Comments on Interrelations between Social Grouping, Mother's Age, Conditions of Conception, Order of Birth of Child, and Arrival of Younger Siblings

From the preceding pages it will be seen that many variables correlate to the children's mental development. The question arises as to what extent these variables are intermingled.

62.5 % of young mothers' children are first-born. The corresponding figures for the intermediate and older groups are 33 and 17 % respectively.

We do not find significant differences between children of mothers in different age groups until the children are 2 years old. At that age the mean quotients of children of older mothers are significantly lower than those of younger. Most of the children of young mothers are first-born but very few (17 %) of those of older mothers. We know that at 2 years of age first-born children have also significantly higher mean quotients than have other children. But at 3 and 5 years high values are no longer found either among the children of young mothers or among first-born.

By 3 years of age 40 children had got younger siblings, the majority or 62.3 % (n = 31) of them being children of young mothers. The quotients of children who had got siblings before the age of 3 years fell significantly from 1 to 3 years compared with children without younger siblings. It is therefore probable that the decline for children of young mothers from 3 years on is partly due to the advent of siblings. The same may be true of the decline in mean quotients for first born between 2 and 3 years, since to a large extent they are the same children.

The young mothers are significantly more often in the lowest social class. Both for the young mothers and for the lowest social group the quotients are lower than the quotients of the intermediate group of mothers and of higher social classes at 3 and 5 years. Both factors may be of importance.

There is no significant age difference between the mothers of illegitimate and of children conceived before wedlock but both groups are significantly younger than the mothers of those conceived after marriage, as we have seen the quotients of the young mothers' children are significantly lower than those of the intermediate group's children at 3 and 5 years. The difference between those conceived after marriage and the others can thus be related to the difference in age of the mothers. The significant difference at 5 years between the illegitimate and the children conceived before wedlock cannot, however, be explained in this way, because the mean age of the mothers in both groups is around 24 years. It may instead be related to the fact that mothers of illegitimate children belong to the lowest social class more often than do mothers, who have conceived before wedlock but married before the child was born.

Summary

The psychomotor (up to 2 years) and mental development of around 200 children as reflected in the Brunet-Lézine and Terman Merrill tests has been followed from 3 months to 5 years in a longitudinal study

In ratings of language development at 3 and 5 years the only significant difference between first born and others is in enunciation (0.05 level) at 3 years (see Table 6).

Ratings were also made of the children's vocal communicativeness from 1 to 5 years of age on a 5-point scale, 1 representing the lowest and 5 the highest degree of communicativeness. First-born and others were compared by χ^2 testing with respect to rated communicativeness. At 2 and 3 years there is a significant difference between first-born and others (0.005 and 0.02 respectively, $\chi^2 = 12.06$ and 8.788, $df = 2$). Also at 18 months there is a tendency in the same direction (0.10, $\chi^2 = 4.718$, $df = 2$). At these ages the first-born are throughout the most communicative. At one and five years the differences are not significant ($\chi^2 = 1.016$ and 2.029, $df = 2$).

Discussion

The better development found in the first-born during the first years is in good agreement with the findings of Bayley [3]. She found in American children tested from 1–15 months of age that first-born compared with others obtained higher scores at 11 ages (of 15). The results may well be due to the fact that parents give greater attention to their first-born.

One reason why the first born are no longer in the lead after the first years may be that by then they have more often got younger siblings. Up to 5 year of age 55% ($n = 46$) of the first-born had got siblings as against 22% ($n = 28$) of the rest.

We have calculated the mean difference between the quotients at 1 and 3 years for children who got or who did not get siblings during their first 3 years of life. In the first group the quotients fell by an average of 8.3 points; in the group without siblings up to 3 years the quotients rose by an average of 2.3 points. The difference between these mean differences is highly significant ($t = 3.49$, 0.001). In the same way the mean differences were calculated from 3–5 years for those who got and those who did not get siblings during that period. In the group who did not get siblings between their third and fifth year the IQ went up by an average of 0.38 point, in the other group it fell by an average of 1.29 points. The difference between these values is not significant ($t = 0.72$).

Relation to Conditions of Conception

Our material includes 23 illegitimate children. We have compared this group with the group of legitimate children.

Results

Table 11 shows that there were no significant differences before the age of 5 years, when the difference is clearly significant in favour of the legitimate children. At 18 months and 3 years there is a tendency in the same direction.

We have also compared children conceived before with those conceived after marriage. At 6 months the children conceived before marriage were significantly more developed than those conceived after marriage. From 18 months the tendency is in the opposite direction and at 5 years the difference is highly significant in favour of the children conceived in wedlock (Table 11).

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By 3 years of age 49 children had got younger siblings the majority or 63.3 % (n = 31) of them being children of young mothers. The quotients of children who had got siblings before the age of 3 years fell significantly from 1 t 3 years compared with children without younger siblings. It is therefore probable that the decline for children of young mothers from 3 years on is partly due to the advent of siblings The same may be true of the decline in mean quotients for first-born between 2 and 3 years, since to a large extent they are the same children

The young mothers are significantly more often in the lowest social class Both for the young mothers and for the lowest social group the quotients are lower than the quotients of the intermediate group of mothers and of higher social classes at 3 and 5 years. Both factors may be of importance.

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Summary

The psychomotor (up to years) and mental development of around 200 children as reflected in the Brunet-Lézine and Terman Merrill tests has been followed from 3 months to 5 years in a longitudinal study

The gestational age of the child is found to be related to developmental level during the 9 first months

Pearsson correlations have been calculated. The correlations between proximate ages are of the order of 0 50–0 75 but diminish quickly with increasing time intervals Like most other authors we have found that tests for infants have little long term predictive value for normal children, but that predictability increases with age

Significant differences between the sexes in favour of girls are present from 18 months to 3 years, most marked at 2 years Girls are more advanced particularly in the language and social sphere This difference is not equally distributed over all social classes, a significant difference between the sexes being found principally within the lowest class. There is a tendency in the same direction within the highest class while no significant differences exist within the middle class.

Significant differences in developmental level were found between social classes. Two types of classification were applied, the Swedish and Graffar s system

At 3 and 6 months the mean quotients of the highest social class are low compared with the middle and lowest classes with the Swedish system of social grouping the differences are significant At 9 and 12 months the classes do not differ significantly From 18 months there are significant differences in the opposite direction the highest class having the higher and the lowest the lower mean quotients. At 3 and 5 years the difference is significant at the 0 001 level on the basis both of Swedish and of Graffar s classification

The socio-economic special scales (occupation mother s education, housing income) were related to developmental level up to 5 years of age A positive relation is earliest manifested in respect of the mother s educational level and the family s occupational status (from 18 months). At 3 and 5 years the children with better conditions in all four scales have significantly higher quotients.

From 3 months to 2 years the motor coordination language and social mean quotients in the development test were related to socio-economic total and partial scales. There are no significant differences in any of the quotients for children living in better than in worse housing conditions.

The group of children whose parents have low incomes compared with those of parents with high incomes are significantly forward in particularly coordination ability at 3 and 6 months, and in respect of social and motor development at 3 months.

Children of parents in the high occupational group have significantly higher coordination quotients at 18 and 24 months than have children of parents in the low group In other respects there is no significant relation between subscale quotients and occupational grouping

As regards the mother s educational level there is an almost significant relation with the child s language development from 12 months of age in favour of the more highly educated group This significance level is successively strengthened at 18 and 24 months. A highly significant relation between mother s educational level and child s coordination ability exists also at 18 and 24 months

The child s development level was related to maternal age At 2 years the mean

quotients of the children of young mothers (<25 years) are significantly higher than those of older mothers children (>32 years). At 3 and 5 years the children of medium-aged mothers (26–32 years) have significantly higher quotients than those of young and older mothers.

First born are more developed than second-born during the first 2 years, the differences between the mean quotients of the first born and second born being significant at 6 9 and 24 months. At 2 years the difference is most marked in the language sphere.

No significant differences in mean quotients between legitimate and illegitimate children exist until 5 years of age when the difference is clearly significant in favour of the legitimate ones. Children conceived before marriage were compared with those conceived after marriage the former being significantly more developed at 6 months. As from 18 months the tendency is reversed and at 5 years the difference is clearly significant in favour of children conceived after marriage.

The child s development level was related to the gainful employment of mothers from 1 to 5 years. No significant differences were found at any age between the mean quotients of the children of gainfully employed mothers and others.

Possible interactions between various social and family factors are discussed.

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APPENDIX I. *Definitions of language rating variables used at 3 and 5 years.*

Enunciation. Clarity and correctness of enunciation of words used (irrespective of vocabulary and syntax)

1	2	3	4	5
Mostly unintelligible	Difficult to understand owing to many faulty sounds or to pervading tendency to mumble.	Most utterance can be understood but are either not very clearly spoken or subject to three or more pervasive childish faults of enunciation.	Generally clear. One or two pervasive childish faults, or occasional lapses or faulty system of enunciation taken over from adults involving slurred or missing consonants.	Clear correct speech sounds throughout (local variations are acceptable if they do not involve corruption of consonant sounds.)

Maturity of language use. To be judged on length and complexity of sentence formation, on vocabulary in use (not Picture vocab. score) and on success in communicating ideas verbally—irrespective of amount of communication attempted.

1	2	3	4	5
Single words only	Elementary sentences, seldom exceeding 3 words, or few longer utterances interspersed with jargon.	Sentences up to 6 or 7 words. Still some difficulty in making meaning clear or attempts at verbal expression distinctly limited.	Simple sentences which are often incomplete, but adequate for most practical purposes. Or correct constructions but limited vocabulary	Mature, correctly worded sentences with vocabulary in advance of the average.

Comprehension of language. Child's evident understanding of what is said to him, as indicated by his responses both in the test and in general conversation. (Distinguish failure to comprehend *from* lack of interest, refusal to co-operate or poor hearing.)

1	2	3	4	5
No apparent comprehension of the simplest instructions (at 3 years defined by: 'Come here', "Give it to me", or parts of body and Identification by Name Tests)	Below average for age. (at 3 years defined by: Fails one or more tests at Year III or below apparently through lack of comprehension of instructions, e.g. Identification by use, Picture Memory—or the equivalent) in other situations)	Average comprehension for age.	Above average for age (at 3 years defined by: Passes 3 of the following 4 tests at III – 6; Simple commands, Comparison of Sticks, Identification by use, Comprehension of questions—or the equivalent.)	Mature intelligent understanding of what is said.

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TABLE 1 *Incidence of breast feeding and time of weaning*

Weaned	n	%	Cumulative n	Cumulative %
Never breast-fed	3	1	3	1
Weaned before ½ month	3	1	6	3
Weaned at 1 month( )	21	10	27	13
2	29	14	56	26
3	23	11	79	37
4	28	13	107	50
5	10	5	117	55
6	23	11	140	66
7	10	5	150	75
8	28	13	163	77
9	12	6	197	93
10	4	2	201	95
11	4	2	205	97
12	4	2	209	99
12½	3	1	212	100

Material and Methods

The material presented here comprises a sample of 21. children, born during the years 1955–1958 living in Solna, a town near Stockholm. For further information of the composition and representativeness of the sample see papers I and II of this series [13, 14].

The analyses comprise the following variables, sex, birth order of the children, mother age social class, educational level, d elling reasons for weaning given by the mothers nd the attitude to breast-feeding and personality traits of the mothers.

The data regarding feeding are based on nterviews with the mothers at the ages of 1 3 6, 9 1., 18 4 30 nd 48 months. (Form 1 columns 31–58) [6] They comprise detailed information of the type of milk, method of feeding and problems connected ith it

All the dat were collected soon after the particular event had occurred Any advice concerning breast-feeding and weaning was given to the mothers through the usual channels, at the Child Welfare Centres, by private practitioners or other means of information.

Results

The Duration of Breast feeding

The incidence of breast-feeding and the time of weaning in the sample are shown in Table 1 and Fig. 1

Three of the babies were never breast-fed, since two mothers had tuberculosis and one baby could not suck. On the other hand 3 children were breast-fed more than 12½ months; one of them received its last breast-feed at 22 months and one at 3 years and 8 months. In both cases these mothers were in the oldest age group (see Table 2) and had several children.

One half of the mothers weaned their children within 4 months (25th percentile for weaning = 1 25/28 month, 75th per centile = 7 months). (See Fig 1) The data do not signify that the babies were exclusively breast-fed up to the time of weaning Some supplementary formula may have been given.

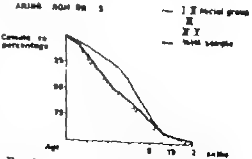

Fig. 1 Breast-feeding cessation. Total sample divided int social classes, according to the Graffar grouping system.

Acta Pædiatrica Scandinavica Suppl 187 94–104 1968

The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study

V Breast feeding and Weaning Some Social psychological Aspects

by G KLACKENBERG and I KLACKENBERG-LARSSON

Introduction

In the investigations of breast-feeding carried out in Sweden in the 1940s and 1950s by Herlitz [8] Nordenfelt [17] Ström [22] v Sydow [23] Mellander Vahlquist & Mellbin et al [15] it was found throughout that the duration of breast-feeding tended to decrease The same observations are reported from other countries in Western Europe and from the U.S.A e g by Douglas [4] Jackson et al [11], and Westropp [24] In the U.S.A the frequency of children who are exclusively breast-fed on discharge from the maternity hospital has decreased from 38 % in 1946 to 21 % in 1956 [16] whereas in Sweden the corresponding figure in 1950 was nearly 95 % and as recently as 1963 it was 83 % [18 19]

The tendency is evident in the annual reports from the Stockholm Municipal Child Welfare Centres Over the past 10 years (1956–1965) the number of babies exclusively breast fed for 2 months has gradually fallen from 69 % to 53 % for 4 months from 40 % to 30 and for 6 months from 26 % to 16 % [1 2]

The cause of this unmistakable decrease is obscure The reasons have been sought in social psychological and biological factors No unequivocal results can be derived from reports of investigations undertaken to throw light on this question. Most of these studies have been retrospective with consequent uncertainty in assessment Hytten & Thomson [10] stress the difficulties in making comparisons, as in many of these studies incomplete data are given on for instance social class, the mother s age civil status and gainful employment and the child s successional number in the family In a recent investigation Hindley et al [9] compared infant feeding in samples from Brussels London Paris, Zürich and ours from Stockholm studied by similar longitudinal methods These studies are coordinated by the International Children s Centre in Paris. The differences in duration of breast-feeding are great even between countries geographically situated as closely as those included in Hindley's et al study The median ages of weaning vary between 0 92 months in the Brussels sample to 4.5 months in the Stockholm sample

As the breast feeding is more common and continues longer in the Swedish group of mothers than it does in any of the corresponding growth-study groups it may be of value to analyse further and separately some social and family factors in association with breast feeding

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3	23	11	79	37
4	[illegible]	[illegible]	107	50
5	10	5	117	55
6	23	11	140	66
7	19	9	159	75
8	26	12	185	87
9	12	6	197	93
10	4	2	201	93
11	4	2	203	97
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One half of the mothers weaned their children within 4 months (.5th percentile for weaning – 1 .5/23 month 75th percentile – 7 months) (See Fig 1) The data do not signify that the babies were exclusively breast fed up to the time of weaning. Some supplementary formula may have been given.

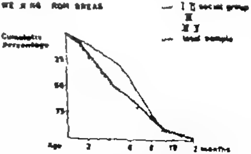

Fig. 1. Breast-feeding cessation. Total sample divided into social classes, according to the *Grellas* grouping system.

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by G KLACKENBERG and I KLACKENBERG-LARSSON

Introduction

In the investigations of breast-feeding carried out in Sweden in the 1940s and 1950s by Herlitz [8] Nordenfelt [17] Ström [22] v Sydow [23] Mellander Vahlquist & Mellbin *et al* [15] it was found throughout that the duration of breast-feeding tended to decrease The same observations are reported from other countries in Western Europe and from the U.S.A e.g by Douglas [4] Jackson *et al.* [11] and Westropp [24] In the U.S.A. the frequency of children who are exclusively breast-fed on discharge from the maternity hospital has decreased from 38 % in 1946 to 21 % in 1956 [16] whereas in Sweden the corresponding figure in 1956 was nearly 95 % and as recently as 1963 it was 83 % [18 19]

The tendency is evident in the annual reports from the Stockholm Municipal Child Welfare Centres. Over the past 10 years (1956–1965) the number of babies exclusively breast-fed for 2 months has gradually fallen from 69 % to 53 % for 4 months from 40 % to 30 % and for 6 months from 26 % to 16 % [1 2]

The cause of this unmistakable decrease is obscure The reasons have been sought in social psychological and biological factors. No unequivocal results can be derived from reports of investigations undertaken to throw light on this question. Most of these studies have been retrospective with consequent uncertainty in assessment Hytten & Thomson [10] stress the difficulties in making comparisons as in many of these studies incomplete data are given on, for instance social class, the mother s age civil status and gainful employment and the child s successional number in the family In a recent investigation Hindley *et al* [9] compared infant-feeding in samples from Brussels London Paris, Zürich and ours from Stockholm studied by similar longitudinal methods. These studies are coordinated by the International Children s Centre in Paris The differences in duration of breast-feeding are great even between countries geographically situated as closely as those included in Hindley s *et al* study The median ages of weaning vary between 0 02 months in the Brussels sample to 4.5 months in the Stockholm sample

As the breast-feeding is more common and continues longer in the Swedish group of mothers than it does in any of the corresponding growth study groups, it may be of value to analyse further and separately some social and family factors in association with breast feeding

Table 3. Duration of breast feeding in relation to sex mother's age social class education and dwelling in subgroups

Subgroups	Sex			Mother' age			Social class (Graffar)			Mother' education		
	Boys		Girls	< 26 yrs		≥ 26 yrs	I + II + III		IV + V	Only elementary school		Others
Sex Boys/girls												
χ^2				2.66		4.99	3.25		2.54	2.60		3.43
Combined χ^2					7.55[a]			5.79[a]			6.03[a]	
p				—	< .05	03	—	—	—	—	< 03	—
Mother age <26/≥26 yrs												
χ^2	8.85		2.78				7.99		0.96	4.41		3.81
Combined χ^2		10.65[a]						8.76[a]			8.22[a]	
p	< 01	< .01	—				01	< 02	—	< .05	< 02	—
Social class I + II/III												
χ^2	6.16		2.00	2.84		4.83						
Combined χ^2		10.19[a]			7.4[a]							
p	.01	.01	—	—	03	< .05						
I + II/IV V												
χ^2	9.94		4.43	1.07		9.67						
Combined χ^2		14.37[a]			10.74[a]							
p	003	.001	03	—	.01	005						
Mother education Only elementary school/others												
χ^2	5.82		1.30	1.30		4.69						
Combined χ^2		6.91[a]			5.99[a]							
p	.05	.03	—	—	05	.03						
Dwelling (in social score 12–18) overcrowded/others												
χ^2				0.068		0.938						
Combined χ^2					1.026[a]							
p				—	—	—						

[a] df 2

secondary school, junior and senior stage or an academic degree continue breast feeding significantly longer than do mothers with only elementary school education.

Since the tested variables may be more or less related χ^2-analyses were carried out with the material divided into subgroups. The variable of the child ordinal position has been excluded as it lacked influence in the whole material. The results are shown in Table 3 and the following conclusions may be drawn.

Sex The fact that boys are breast-fed longer than girls is most marked in the mothers of the higher age-group and in the mothers with higher education. The combined χ^2 values within these variables are significant at the 0.05 level. A tendency in the same direction is also seen in social classes I + II + III.

Age The tendency for young mothers to

TABLE 2 *Duration of breast feeding related to some family and social factors*

	n	Last breast feed: Before or at 4 months %	Last breast feed: Later than 4 months %	χ^2		p
Sex						
(a) Boys	120	43	68	a/b	5.94	02
(b) Girls	89	60	40			
Ordinal position						
1st born	83	51	49			
2nd born	89	50	49			
3rd and subsequent	38	45	55			
Mother s ge						
(a) < 25 yrs	87	62	38	a/b + c	9 03	< 005
(b) 26–32 yrs	88	40	60	a/b	9 09	< 005
( ) ≥ 33 yrs	34	44	56	a/c	2 44	< .20
Social class (Graffar)						
(a) I + II	52	27	73			
(b) III	64	55	45	a/b	9 05	< .005
( ) IV + V	93	59	41	a/c	13 88	< .001
Mother s educational level						
(a) Only elementary school	143	56	44	a/b	6 92	< 01
(b) Others	66	36	64			
Dwelling in Graffar social score 13–29						
( ) Overcrowded	42	52	48	a/b	0 09	—
(b) Others	86	62	38			
(a) Modern flats	77	49	51	a/b	6.39	< [illegible]
(b) Others	50	72	28			

Relationship between weaning and various family and social data

In analysing the data (by the χ^2 method) the sample has been dichotomized near to the median value for duration of breast-feeding Mothers who have given the last breast-feed at 4 months or earlier are referred to the category of earlyweaners and the others to lateweaners

Table 2 shows the relation to sex birth order of the children mother s age social class educational level and dwelling There is a sex difference the boys being breast fed longer than the girls ($p < 0\,02$) but no difference in relation to birth order With the mothers divided into 3 age-groups, 25 years or younger 26–32 years and 33 years or more only the difference between the youngest and the intermediate age-group (or the two oldest age-groups) is significant ($p < 0\,005$) As regards the social grouping by Graffar s system the mothers in social class I + II continue breast-feeding longer than the mothers do in social classes III and IV + V The difference is significant at the 0 001 level between I + II and IV + V and at the 0 01 level between I + II and III

Mothers with the higher education

U.S.A a shift is reported [3] from earlier longer breast-feeding periods in low socio-economic groups to longer period for middle class Contradictory results have been obtained in England [0] The results reported from Belgium [20] and Sweden [17] agree with ours, namely a long duration of breast-feeding in the highest social class.

Mothers Reasons for Weaning

The mothers were asked about their reasons for weaning For mothers, who weaned their children before or at 6 months, the predominating reason was "no or insufficient milk In about one-third this was the only reason given. No or insufficient milk together with the child s refusal to take the breast or preference for other milk was the most common combination Tiredness and nervousness, etc were the reasons in just over one-fourth of the 127 mothers; medical obstacles to breast feeding, such as sore or inflamed nipples, play a relatively minor role and were st ted only by mothers who weaned their babies in the first two month

As regards gainful employment as a reason for weaning it is evident that the desire to resume work or to start working plays no mport nt role in the falling in cidence f breast feeding This will be seen from the mere fact that 6 (full time) of the mother our sample were gainfully employed t the time (4 months), hen 50 of the children had been eaned Only 3 f the mothers gave g inful employment a reason.

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The complexity of the factors of psychic nd physiological nature involved in breast-feeding makes it difficult to analyse the variables influencing weaning We are concerned here with processes that are *only in part* controlled by the conscious will of the mothers. It may therefore be questioned to what extent the mothers answers to direct inquiries of this nature would supply complete information about the reasons for weaning Furthermore a mother who does not breast-feed her baby for the length of time advised by the Child Welfare Centres, would presumably be inclined to feel guilty especially if she gives up breast-feeding for reasons that are not regarded as acceptable

In more primitive societies the duration of breast-feeding is considerably longer [25]; the falling frequency of breast-feeding seems mostly t be a phenomenon of Western civilization. This continuous process has been faster in some Western countries than in others.

The Mothe s Attitude to Breast feeding and to Weaning

During the period of breast feeding the interviewer asked the mothers how they liked it The answers were graded as positive indifferent and negative" The statement that the breast-feeding made them tired was also in luded among the nswers

Judged by their statements most of the mothers had a positive attitude to breast feeding both t the 1 month (69 %) and at the 3-month (77 %) interview The greater percentage of mothers who at the later interview stated that they liked breast-feeding is related to the fact that the majority (8 of 1°) of those with a negative attitude *at 1 month had* stopped weaning before 3 months.

stop breast-feeding earlier than the others is seen in all the subgroups (when calculated separately) with the exception of Graffar's lowest social class The combined χ^2 values within the three variables sex, social class and mother's education are all significant at least at the 0 02 level

Social class The differences between social classes are most prominent among boys and among the intermediate and older groups of mothers. The combined χ^2 values within the variables sex and mother's age are both significant at least at the 0 01 level for the difference between classes I+II versus IV+V and at least at the 0 05 level for the difference between classes I+II versus III

Education. The significance levels for the differences between the mothers in the two educational groups are valid only for the boys and the intermediate and older groups of mothers The combined χ^2 values within the variables sex and mother's age are both significant at the 0 05 level

Dwelling Overcrowding (≥ 2 persons per room) is most common in the lower social classes These include more young mothers in our sample There is no significant difference in the duration of breast feeding between the overcrowded group at a lower social level (Graffar social score 13–20 lowest category) neither for young nor for older mothers A comparison within social score 13–20 between mothers in modern flats (hot and cold water w c bathroom) and those in old fashioned flats shows however a significant difference at the 0 02 level between the groups ($\chi^2 = 6.39$) Those who live in old fashioned houses wean their children earlier

Comments

The results of the different analyses (Tables 2 and 3) can be summarized as follows. The duration of breast feeding is found to be related to each of the factors sex mother's age and social class. The boys, the children of medium and older mothers and the children in the highest social class are breast fed longest Mothers with higher educational level and mothers (in social score 13–20) living in modern flats breast feed their children longer than do others —No relation to birth order was found

Nordenfelt [17] in his investigation of materials from the Child Welfare Centres in Stockholm reported that the first-born were breast-fed longer Herlitz [8] found no significant differences but a tendency in the opposite direction Both studies however include only married mothers. Moreover as Nordenfelt excluded those who are gainfully employed their investigations are not fully comparable with ours. Dykes [5] states that family size has little influence on the duration of breast feeding which is in accordance with our findings. His investigation comprised all children ($n = 1403$) born in 1945 in a town in England

The observation that young mothers breast feed for a shorter time has earlier been made in some comprehensive Swedish investigations by Herlitz and Nordenfelt [8 17] This relation to mother's age however does not seem to be generally found in other countries [9]

The relation to social class seems by no means to be a simple one different results have been reported from different countries and at different periods of time From the

U.S.A a shift is reported [3] from earlier longer breast-feeding periods in low socio-economic groups to longer period for middle class. Contradictory results have been obtained in England [9] The results reported from Belgium [20] and Sweden [17] agree with ours namely a long duration of breast-feeding in the highest social class.

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The complexity of the factors of psychic nd physiological nature involved in breast-feeding makes it difficult to analyse the variables influencing weaning We are concerned here with processes that are only in part controlled by the conscious will of th mothers It may therefore be questioned to what extent the mothers answers to direct inquiries of this nature would supply complete information about the reasons for weaning Furthermore a mother who does not breast-feed her baby for the length of time advised by the Child Welfare Centres would presumably be inclined to feel guilty especially if she gives up breast feeding for reasons that are not regarded as acceptable

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Very few mothers show persistently an indifferent or negative attitude There are many variants of the answers in the positive group such as restful delightful the best time of the day relaxing But the pleasure in breast-feeding is no guarantee against early weaning even though it would be expected to signify a more favourable prospect than the sufferings that some mothers describe such as giddiness headache waste of time nervousness pain and extraordinary tiredness An analysis of the total sample for a possible relation between time of weaning and declared attitude to breast-feeding at 1 month did not however give any significant results

When the breast feeding period was over the mothers were asked whether they felt relieved. The answers were classified as follows Did not like to stop breast-feeding indifferent ambivalent relieved.

The mothers reactions to the fact that the breast-feeding period had come to an end were fairly similar in those who weaned their children before and after 6 months About half (50 % and 54 %, respectively) were pleased with the situation They felt relieved and were glad that the breast-feeding period was over In some cases words such as tiring and wearisome accompanied the answers as an explanation On the other hand about one fourth (27 % and 22 %, respectively) of the early weaning and the late-weaning group did not like to stop breast feeding Some expressed regret a feeling of having lost something that was valuable of not having the baby to themselves as much as before The most likely interpretation of the fact that so many of the mothers who had continued breast feeding for at least 6 months did not feel relieved at the time of the last breast-feed might be that to those mothers breast-feeding was a pleasure rather than a duty

Comments

It may be questioned how far the mothers answers express what they really feel and not what they think one should feel if one wants to be regarded as a good mother The interviewer often felt that the positive answers to breast-feeding were given without any great enthusiasm It may seem somewhat odd that so many positive breast-feeders felt cessation as a relief

Duration of Breast feeding and Weaning Troubles

The mothers were asked about the child s response to weaning The answers were divided into three groups by the degree of weaning difficulty and graded as difficult moderate and easy" The duration of breast feeding dichotomized at 4 months was analysed in relation to the degree of difficulty in weaning using the χ^2 test The answers difficult" and moderate were brought together into one group versus the easy group

The children who were difficult to wean were those who were breast-fed longest The difference is significant at the 0 01 level ($\chi^2 = 8\ 08$)

When calculated for boys only the difference is still significant at the 0 01 level (χ^2 8 40) but for the girls alone it is not significant (χ^2 0 01)

Comments

The fact that weaning at a later time is regarded as more difficult may be related

TABLE 4 *Ratings of personality variables and duration of breast feeding*

Duration of breast feeding	Self-confidence		Security		Orderliness		Temperament	
	1+2	3–5	1+2	3–5	1+2	3–5	1+2	4+5
3 mos. or shorter	7	[illegible]	8	[illegible]	20	56	25	16
6 mos. or longer	29	[illegible]	23	[illegible]	45	49	22	37
χ^2	10.88		5.48		8.27		10.78	
p	$< .001$		$< .02$		$< .01$		$< .005$	

to the fact that the habit of sucking has become more deep-rooted and then is more difficult to terminate.

That this relation only holds true for the boys is perhaps related to the tendency of the mothers to breast feed the boys longer

Duration of Breast feeding and Mother's Personality

At each interview the psychologist tried to rate some traits of the mother's personality on 5-point scales. The ratings of the mothers who had breast fed their babies for the first 3 months were compared with those who had continued for at least up to 6 months. We used the rating scale units which were most common for a mother during the first 2 years. The mothers who were rated equally often as e.g. points 2 and 3 were randomly distributed between 2 and 3

The rated variables were self-confidence, security, orderliness and temperament. The scale unit for self-confidence range from "highly self-confident" (1) to "diffident" (5). Mothers rated as having great or fairly great self-confidence (1+2) were compared with the others. For the variable "orderliness" the scale unit range from "pedantic" (1) to "careless" (5). Those rated "pedantic" and "orderly" were brought together into one group which was compared with the others. As regards the variable "temperament" those rated as "quick tempered" and "lively" (1+2) were compared with those rated as "calm" and "slow" (4+5).

Table 4 shows the distributions, χ^2 and p-values

Comments

The mothers who had continued breast-feeding for 6 months or longer have more often been rated as more self-confident, secure, orderly and calm. It is perhaps not surprising that mothers with these qualities breast feed longer than others.

Night feeds in Infancy

According to the principles in the maternity wards the infants are not given night-meals. The children of the sample were born in different maternity hospitals and in none of the cases do the collected data indicate that they were treated differently in this respect from newborn babies in general. The picture changes after the return home from the hospital. Fig. 4 shows the percentage of infants who were given night meals at various ages, that is, who were fed (at the breast or from a bottle) some time between midnight and

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The children who were difficult to wean were those who were breast fed longest The difference is significant at the 0 01 level ($\chi^2 = 8\ 98$)

When calculated for boys only the difference is still significant at the 0 01 level ($\chi^2 = 8\ 46$) but for the girls alone it i not significant (χ^2 0 01)

Comments

The fact that weaning at a later time is regarded as more difficult may be related

analysed for their association with various social and family factors and personality variables in the mothers. The following statistically significant relationships were found 1 Boys are breast-fed longer than girls. 2. Mothers in the higher age-group (26 and over) continue breast-feeding longer than do younger mothers (under 26). 3 Mothers of the highest social class (Graffar I + II) continue breast feeding longer than do mothers in the intermediate (Graffar III) and the lowest (Graffar IV + V) social classes. 4. Mothers with higher education continue breast-feeding longer than do mothers with only elementary school education. 5 In the lowest social class mothers who live in old-fashioned houses stop breast feeding earlier than do mothers living in modern houses. 6. Some personality traits of the mother are more often than others associated with long-continued breast-feeding

No statistical relationships were demonstrated between the duration of breast feeding and overcrowding or the child's successional number in the family

The reasons for weaning were analysed "No or insufficient milk" was the most common reason given by mothers who weaned their babies before 6 months Gainful employment was of very little importance as a reason for weaning.

The mothers attitudes towards breast-feeding in the child's first and third months of life were generally positive. The duration of breast-feeding cannot be predicted from the attitude declared by the mothers.

The frequency of night-feeding on the return home from the maternity hospital was 85 % and at 3 months 25 %. The boys received night meals for a significantly longer period than did the girls. The mother's age, the child's successional number in the family social class, the duration of breast feeding and the mother's attitude to breast-feeding showed no association with the continuation of night-feeding.

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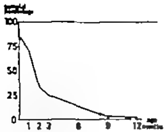

Fig 2. Night meal cessation (n = 212).

5 o clock a m It will be seen that 85 % of the babies received night-meals

Information about the time of cessation of night-feeding was obtained from the mothers at the interviews following her return home In some cases night-feeding started later than the first month of life or ceased for a time to begin again later As a rule however it was continued fairly uniformly (with a shift towards early morning) up to the time when there was no longer any need for it and the child began to sleep through. In other cases the child could wake once or a few times a week during the transitional stage This was usually accepted by the mother as an expression of the child s need of a feed More or less successful attempts to avoid feeding the baby in the night were reported by some mothers Fear of disturbing the rest of the family and the neighbours was in some cases stated to be the reason for keeping the child quiet by a night-feed.

Seventy five per cent of the children had finished their night-mealperiod at the age of 3 months The group of 60 children who had never got a night-meal or had had the last one at or before the age of 1 month was compared in various respects with those 50 children who had retained the habit of having night feeds for more than 3 months The comparison concerned the association between night feeding and the child s sex the mother s age the child s successional number in the family (first child versus others) social class (as defined in Sweden) and the duration of breast-feeding (longer or shorter than 4 months) The two groups compared differed only with respect to the association with the child s sex 36 % (n = 44) of all the boys belonged to the group with night feeds for more than 3 months. The corresponding figures for the girls were 16 (n = 14) The percentage difference is 20 ± 6.3 significant at the 0 001 level

Comments

The sex difference found admits of different interpretations of a speculative nature It may be thought to be associated with more activity together with greater need of nourishment in the boys. But differences in caloric requirements between boys and girls of this age are not known. The basal metabolism in relation to body size shows no difference between the sexes [12] If the differences found can not be assigned to the child s biological characteristics the continued practice of night feeding could be associated with the mothers attitudes to boys. The mothers may be thought to have more positive attitude to them than to girls. Conscious as well as unconscious desires may play a part

Summary

Data on breast-feeding weaning and the practice of giving night meals, collected in the prospective longitudinal growth study presented earlier have been

analysed for their association with various social and family factors and personality variables in the mothers. The following statistically significant relationships were found. 1 Boys are breast fed longer than girls. 2. Mothers in the higher age-group (26 and over) continue breast-feeding longer than do younger mothers (under 26). 3 Mothers of the highest social class (Graffar I+II) continue breast-feeding longer than do mothers in the intermediate (Graffar III) and the lowest (Graffar IV+V) social classes. 4. Mothers with higher education continue breast-feeding longer than do mothers with only elementary school education 5 In the lowest social class, mothers who live in old fashioned houses stop breast-feeding earlier than do mothers living in modern houses. 6 Some personality traits of the mother are more often than others associated with long-continued breast-feeding

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The reasons for weaning were analysed "No or insufficient milk" was the most common reason given by mothers who weaned their babies before 3 months. Gainful employment was of very little importance as a reason for weaning

The mothers attitudes towards breast-feeding in the child first and third months of life were generally positive The duration of breast-feeding cannot be predicted from the attitude declared by the mothers

The frequency of night-feeding on the return home from the maternity hospital was 85 % and at 3 months 25 %. The boys received night meals for a significantly longer period than did the girls The mother s age, the child s successional number in the family social class, the duration of breast-feeding and the mother s attitude to breast-feeding showed no association with the continuation of night-feeding

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Fig. 2. Night meal cessation (n = 21).

5 o'clock a.m. It will be seen that 85 % of the babies received night-meals.

Information about the time of cessation of night-feeding was obtained from the mothers at the interviews following her return home. In some cases night-feeding started later than the first month of life or ceased for a time to begin again later. As a rule, however, it was continued fairly uniformly (with a shift towards early morning) up to the time when there was no longer any need for it and the child began to sleep through. In other cases the child could wake once or a few times a week during the transitional stage. This was usually accepted by the mother as an expression of the child's need of a feed. More or less successful attempts to avoid feeding the baby in the night were reported by some mothers. Fear of disturbing the rest of the family and the neighbours was in some cases stated to be the reason for keeping the child quiet by a night-feed.

Seventy five per cent of the children had finished their night-mealperiod at the age of 3 months. The group of 60 children who had never got a night meal or had had the last one at or before the age of 1 month was compared in various respects with those 50 children who had retained the habit of having night-feeds for more than 3 months. The comparison concerned the association between night feeding and the child's sex, the mother's age, the child's successional number in the family (first child versus others), social class (as defined in Sweden) and the duration of breast-feeding (longer or shorter than 4 months). The two groups compared differed only with respect to the association with the child's sex. 36 % (n = 44) of all the boys belonged to the group with night feeds for more than 3 months. The corresponding figures for the girls were 16 % (n = 14). The percentage difference is 20 ± 6.3, significant at the 0.001 level.

Comments

The sex difference found admits of different interpretations of a speculative nature. It may be thought to be associated with more activity together with greater need of nourishment in the boys. But differences in caloric requirements between boys and girls of this age are not known. The basal metabolism in relation to body size shows no difference between the sexes [12]. If the differences found can not be assigned to the child's biological characteristics, the continued practice of night feeding could be associated with the mothers' attitudes to boys. The mothers may be thought to have more positive attitude to them than to girls. Conscious as well as unconscious desires may play a part.

Summary

Data on breast feeding, weaning and the practice of giving night meals, collected in the prospective longitudinal growth study presented earlier, have been

analysed for their association with various social and family factors and personality variables in the mothers. The following statistically significant relationships were found. 1 Boys are breast-fed longer than girls. ... Mothers in the higher age-group (26 and over) continue breast-feeding longer than do younger mothers (under 26) 3 Mothers of the highest social class (Graffar I+II) continue breast-feeding longer than do mothers in the intermediate (Graffar III) and the lowest (Graffar IV+V) social classes. 4. Mothers with higher education continue breast-feeding longer than do mothers with only elementary school education. 5 In the lowest social class, mothers who live in old fashioned houses stop breast-feeding earlier than do mothers living in modern houses. 6 Some personality traits of the mother are more often than others associated with long-continued breast-feeding

No statistical relationships were demonstrated between the duration of breast feeding and overcrowding or the child s successional number in the family

The reasons for weaning were analysed. "No or insufficient milk was the most common reason given by mothers who weaned their babies before 6 months. Gainful employment was of very little importance as a reason for weaning

The mothers attitudes towards breast-feeding in the child s first and third months of life were generally positive The duration of breast-feeding cannot be predicted from the attitude declared by the mothers

The frequency of night-feeding on the return home from the maternity hospital was 85 % and at 3 months 25 %. The boys received night-meals for a significantly longer period than did the girls. The mother s age the child s successional number in the family social class, the duration of breast-feeding and the mother s attitude to breast-feeding showed no association with the continuation of night-feeding

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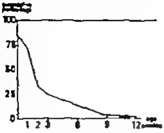

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Acta Pædiatrica Scandinavica Suppl. 187 105–121 1968

The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study

VI The Sleep Behaviour of Children up to Three Years of Age

by G KLACKENBERG

Introduction

The sample comprises 12 children, followed from birth onwards. Concerning the course of the study up to the time children are 3 years of age the reader is referred to the general introduction, given in paper I of this series [9].

The results reported here relate to the length of sleep at different times during the children first 3 years of life and to sleep disturbances during the same period.

The data are based on the mother's observations By the standardized interviews information was obtained of the child's sleep not only at the visit but also in the intervals between the visits The values thus attained can therefore form the basis for a cross-sectional analysis and also for long range view of the sleep behaviour of the individual children. In a cross-sectional analysis an occasional waking in the night for example will in the statistical calculations carry the same weight as persistent wakefulness It is only by the longitudinal analysis that the habitual sleep-behaviour of the individual subjects will emerge By recording the event soon after it occurred, the prospective longitudinal method gives smaller margins of error than do retrospective studies [14].

The information obtained concerning sleep will be seen in interview form part II, columns 47–78 [3]. The first two questions are of introductory type their aim being to find out, in general terms, what the mother thinks of the child's sleep and how the sleep disturbances, if any manifest themselves. The next six questions concern bedtime waking time length of sleep, number of day time naps and their duration, and whether these factors show any regularity The next 18 questions relate to the child's behaviour at bedtime, during the first few evening hours, and in the night These inquiries also include the measures taken by the parents in case of trouble. The rest of the questions concern the child's sleeping conditions, such as the bed, bedroom etc

These provided a basis for a numerical description of data and, in the treatment of several items, statistical analysis as well. The latter comprised, in particular prediction and correlation with other data of social somatic, or psychic nature [3 6].

The account will be divided into four main sections.

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The account will be divided into four main sections.

TABLE 1 *The mothers opinion of the children s sleep at various ages in general terms Percentage distribution*

Age (months)	1 (n = 162)	3 (n = 187)	6 (n = 197)	9 (n = [illegible]01)	12 (n = [illegible]08)	[illegible] (n = 194)	4 (n = [illegible]04)	36 (n = [illegible]06)
Not well	8	3	7	10	16	16	1	4
Fairly well	[illegible]	[illegible]	17	15	13	14	14	16
Very well	71	78	72	74	70	68.5	7	77
Extremely well	3	6	4	1		1.5	2	3

I The mother s general opinion of the child s sleep
II Length of sleep
III Bedtime behaviour
(a) Resistance to bedtime preparation
(b) Evening wakefulness
(c) Night waking
IV Night disturbances during long periods

I The Mother s General Opinion of the Child s Sleep

The answers to the introductory question concerning the mother s general opinion of how the child sleeps were graded as extremely well very well fairly well and not well Table 1 giving the percentage distribution of the answers shows to what extent the mothers find their children s sleep good or not good at different ages. It is a total impression of both day and night sleep including duration of sleep waking and troubles of various kinds.

In Fig 1 the percentage distribution of the gradings that have negative signs (not well and fairly well) is plotted against age separately and taken together At the age of around 3 months the children s sleep behaviour evidently deviates least and at 12–18 months most from the ideal of a long and unbroken sleep [13] At some ages, this curve does not correspond to the true incidence of night waking (cf Fig 6 page 115) As for the one month-old children, most mothers apparently consider it quite natural for the children to wake up in the night (75% have night feeds, cf [11]) and do not always regard this as bad sleep The wakefulness is accepted as part of the sleep pattern at this age. Another deviation from the true frequency of night waking is found at 3 years Many of the children will then wake because of an urge to pass water and/or because they wish to get into the parents beds. This is in many cases not regarded as bad sleep. It is presumably the degree of inconvenience experienced by the mother that determines if she will feel the awakening as a sleep disturbance A break or an interruption of the child s sleep is not always

TABLE 2 *Main groups of complaints on sleep behaviour as a percentage of complaints at four different ages*

Age (months)	3	9	18	36
Night waking	[illegible]	44	63	[illegible]
Poor day sleep	38	28	2	0
Evening wakefulness	0	17	18	28
Resistance to bedtime preparations	0		12	30
Various (light restlessness, night terrors)	0	9	10	14

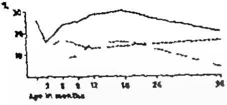

Fig. 1 The mothers' general opinion of the children sleep at various ages. 1 percentage of children with bad sleep; 2 percentage of children with fairly good sleep; 3 total percentage for 1 + 2.

recognized as a sleep disturbance from the family's point of view: the terms are not always identical. The tolerance of the mothers can also vary according to their personal make-up. These considerations should be borne in mind for the detailed study of the sleep behaviour that will be presented in a subsequent section.

The troubles that the mothers have with their children s sleep vary somewhat with respect to nature and content from time to time. This is best illustrated by Table .., which shows the frequency of the main groups of complaints at four different ages (3 9 18 and 36 months)

Night waking is the predominating complaint about the child's sleep. But for the first year of lif a strikingly large group of mothers are of the opinion that the children sleep too little in the daytime. Resistance to bedtime preparations as well as waking after a short spell of sleep become increasingly common with increasing age and re t 3 years as great a cause of worry as is the night waking.

II Duration of Sleep

Total length of sleep per 4 hours The assessment of the children s total length of sleep per 24 hours is based on a detailed questionnaire and, with the aid of the stated bedtimes and awakening times, the replies provide a value for the length of sleep at different ages.

Fig. * shows the bedtimes and awakening times at 1 * and 3 years. Great individual variations are seen at all age-levels. Some children fall asleep habitually at 6 p.m whereas others are not ready for their night s sleep until 10 o clock. Similarly the within-group variation in the awakening time ranges over a period of 4 hours The children who go to sleep early are not always found among the early wakers, and vice versa although the cumulative percentage curves for the group run a strikingly similar course. At each age-level, there are in fact big differences for the length of sleep with the highest

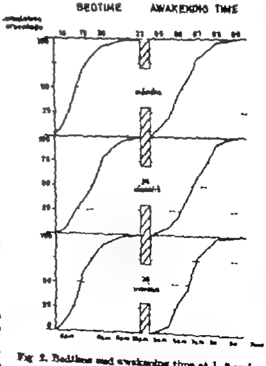

Fig 2. Bedtime and awakening time at 1 2 and 3 years of age.

TABLE 3 *Length of sleep at different ages (means and standard deviations)*

Age (months)	6	9	12	18	24	36
Day sleep						
Percentage of children with day sleep	100	100	99.5	97	79	[illegible]
Means of hours[a]	3 7	2.5	[illegible]	1.5	1.3	[illegible]
S.D	±1.5	±1.1	±0 8	±0 66	±0.55	±0 64
Night sleep						
Means of hours	10 6	11 0	11.2	11 4	11.2	11 4
S.D	±1 1	±1.2	±1 1	±1.2	±1.3	±1 0
Total length of sleep (day plus night)						
Means of hours	14.3	13.5	13.2	12.8	12.4	11.9
S.D	±1 7	±1.4	±1.3	±1 1	±1 0	±1 0
	(n = 199)	(n = 202)	(n = 207)	(n = 196)	(n = 203)	(n = 206)

[a] Refers to children who still sleep in the daytime.

standard deviations at 6 months of age as shown in Table 3 and Fig 3

The figures in Table 3 refer to the average number of sleep hours per day and per night as well as totally We are concerned here with sleep hours as far as the parents could tell that the child was asleep If the child lies awake in the night the number of sleeping hours was reduced by the lying awake time Numerical values for the length of sleep from the observations at 1 and 3 months were not included The reason for this omission is that it is often extremely difficult to make a sharp definition between sleep and wakefulness in the child's first few months of life. At times the children often lie half asleep and an attempt at condensing the information supplied by the mothers into average values for this age level would imply a seeming exactness. Sources of error of such a gross nature have been avoided.

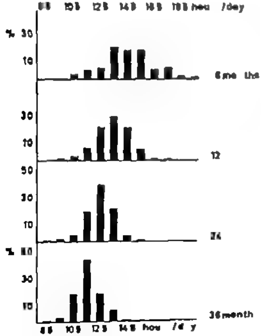

Fig 3. Total sleep in hours/day at different ages.

That the total length of sleep decreases with age is a well known fact During the period 6 months–3 years the decrease of the 24-hour sleep averages about 2½ hours This reduction of the total length of sleep does not depend upon a decrease of the length of the night sleep which varies only slightly but upon a decrease of the length of day sleep For further analysis of the relationships between day and night sleep the reader is referred to a later section of this paper (cf pages 110–111)

Relation between the length of sleep at

different ages in the same child To find out whether the length of sleep of a particular child would provide any forehand information as to the length of his sleep at a later age, the correlation between length of sleep at different ages in the same child was calculated. The results are set out in Table 4

There are correlations, most of them not due to chance between the length of sleep at different ages during the period 6 months–36 months. The correlations are however of a low degree. Accordingly the possibilities to predict the later total length of sleep of a particular child from an earlier observation are small.

Relation of length of sleep to season. To find out whether there are any seasonal variations in the length of sleep, the correlation between the total sleep and the average number of day light hours in the months of the year was calculated for the different age-levels. As the children were observed on, shortly before or after their birthdays, this correlation could be studied for the length of sleep at 12 24 and 36 months There was no significant relationship. The correlation coefficients for the respective ages were − 04 12 and .09 (cf. also page 111 concerning relation of night-sleep t season)

Length of sleep and living space The analysis concerns differences in length of sleep between children t 1 year under different d elling conditions. A division was made into short sleepers (9–13 hours) and long sleepers (15–20 hours) representing two groups of the same size distributed around the mean. "Over crowding' denotes that the family's living space allows as a maximum half a room per person As an example may be mentioned that the most common accommodation that refers the studied families to the category of overcrowded" consists of one room plus a kitchen (the kitchen is counted as a room if large enough to be used for meals and for sleeping purposes) for two parents and two children, that is, four persons. The object of the analysis was to find out whether disturbances from the environment due to overcrowding might reduce the effective sleeping hours. No difference in this respect was found for the children at 1 year of age The χ^2 value was 0.055

TABLE 4 *Correlation coefficients of length of sleep at different ages*

Age (months)	9	12	18	24	36
6	.28	.22	.26	16	(14)
9		.23	.27	18	(14)
12			40	(13)	15
18				.26	(00)
24					.29

Parentheses signify correlations which do not differ significantly from 0.

$*** = p < .001$; $= p < .01$ $= p < .05$.

Similar analyses at 2 and 3 years gave χ^2 values of 1.24 and 0 008, respectively "Long sleepers and short sleepers" refer to the group of children on each side of the group containing the mean value (cf Fig 3). The limits for overcrowding" were here less narrow Families occupying up to three-quarters of a room per person were referred to this category Thus, the results do not demonstrate any correlation between the length of the child s sleep and overcrowding as defined here.

Length of sleep of children whose mothers are gainfully employed The length of sleep of children at the age of 1 year whose mothers were gainfully employed did not

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Age (months)	6	9	1	18	4	36
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Percentage of children with day sleep	100	100	99 5	97	79	23
Means of hours[a]	3.7	2.5	0	1.5	1.3	1..
S.D	±1.5	±1 1	±0 8	±0 66	±0.53	±0.66
Night sleep						
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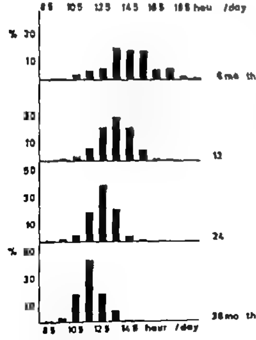

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Length of sleep and living space. The analysis concerns differences in length of sleep between children at 1 year under different dwelling conditions. A division was made int short sleepers (9–13 hours) and "long sleepers (15–20 hours), representing tw groups of the same size distributed around the mean. Overcrowding denotes that the family's living space allow as maximum half room per person. As an example may be men

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Length of sleep of children whose mothers are gainfully employed The length of sleep of children at the age of 1 year whose mothers were gainfully employed did not

TABLE 5 *Correlation between length of sleep and mental development quotient*

	n	*r*	*p*
At 6 months	193	− 4	< 001
9	02	− 13	< 10
12	*05	− 13	< 10
18	195	− 03	—
24	0?	− 05	—
36	*03	08	—

differ significantly from that of the children whose mothers did not go out to work ($\chi^2 = 2\ 360$) ('long-sleepers' versus 'short-sleepers' cf above)

Relation of length of sleep to mental development quotient The correlations between the children's total length of sleep and the developmental quotient obtained by Brunet-Lezine's development test at each interview are shown in Table 5 At 36 months the Terman–Merrill intelligence test was used It will be seen that a weak negative correlation exists only at 6 months At the other tested age-levels the connection can be neglected.

Day sleep–night sleep Day sleep is here defined as the sleep that occurs after the family and the child have awakened in the morning and up to the time usually between 5 and 7 o'clock in the evening when the child goes to sleep for a longer stretch. In general it was easy to apply this definition when the children had reached the age of 6 months But even after 6 months it seemed in some cases uncertain whether the sleep periods in the afternoon and early evening were to be counted as day or night sleep For example a child who sleeps from 4 to 7 p m but then stays awake for several hours to enter his longest stretch of sleep after say 10 p.m was considered to "settle for the night" at the latter hour On the other hand in the case of a child who having settled at 6 p m. wakes up for his evening meal at 10 p.m and then goes to sleep again the child's night sleep was counted as from 6 p m This problem of definition does not of course affect the total length of sleep discussed in previous sections, but will be of significance in the study of changes in the day sleep and the night sleep respectively

Earlier studies [1 2 4 7 12] have shown that the infant's sleep periods during the first few weeks of life are more evenly distributed over the twice-round-the-clock period. A distinct day–night rhythm cannot be discerned. The change over to a 24-hour pattern with longer night and shorter daytime periods of sleep occurs gradually According to Hellbrügge [8], a typical day–night pattern can be observed at the age of 4 weeks, but not until the end of the first year of life can it be considered to be fully developed. Because of the irregularities during the first months of life it has proved difficult by the methods used in this study to obtain accurate values from the ages of 1 month and 3 months. For this reason the data reported below refer to the observations at 6 months and subsequent interviews up to 36 months

Means and standard deviations for the number of hours of day sleep can be seen in Table 3 (page 108) These hours are distributed among the number of sleep periods set out in Table 6 (for the ages 6 12 24 and 36 months)

The need of a nap in the daytime seldom disappears suddenly from one day to another The break-off is usually preceded

TABLE 6. *Percentage distribution of sleep periods in the day at different ages*

Number of sleep periods in the day	Age (months)			
	9	[illegible]	24	36
0	[illegible]	0 5	21	77
1	8	55	[illegible]	23
2	40	41	1	0
3 or more	52	3.5	0	0

TABLE 7 *Correlation between day sleep and night sleep at different age-levels*

Age (months)	n	r	p
9	200	−.21	<.01
12	203	− [illegible]	<.01
18	194	−.16	<.05
24	198	−.37	< .001
36	168	−.33	<.001

by a period of vacillation between having a nap in the daytime and going to sleep earlier in the evening.

The age at which day sleep is abandoned varies individually Most of the children in the sample passed through this stage between the ages of 2 and 3 years. Among the three-year-old, only 23% has a nap during daytime.

Relation between length of day sleep and length of night sleep It will be seen from Table 7 that there is a correlation between the length of day sleep and the length of night sleep at different ages.

The tendency that can be discovered from Table 7 may be summarized as follows: As the child curtails its sleep by day it lengthens its period of continuous night sleep correspondingly As can be seen, the correlations are not due to chance. They become stronger when the child reaches the age of 2–3 years.

Relation between the length of night sleep at different ages in the same child This analysis is based on the presumption that the children gradually develop a certain sleep pattern—in this case with respect to night sleep—which remains a characteristic A child that at a certain age sleeps for relatively long time in the night may provided that the presumption is correct be expected to have the same relative need of sleep at a later age This analysis therefore concerns the predictability as regards the length of night sleep

Evidently in the nine-month-old the night sleep has not yet reached the stability which affords a meaningful association with later ages (table 8). From the age of 12 months there are significant correlations to the following ages concerning the night sleep

Relation of night sleep to season. In a similar way as concerning seasonal influences on the total sleep duration (cf. page 109) the correlation coefficients of the night-sleep hours and the average of daylight hours were computed. The coefficients indicate that the children slept shorter in the summer nights at 2 and 3 years of age but the negative correlation

TABLE 8 *Correlation coefficients of length of night sleep at different ages*

Age (months)	12	[illegible]	24	36
9	.15	(.01)	(.11)	(.11)
12		.31	.26	.42
18			.16	.22
24				.49

Parentheses signify correlations which do not differ significantly from 0.

$^{**} = p < .001$; $^{*} = p < .05$.

TABLE 5 *Correlation between length of sleep and mental development quotient*

	n	r	p
At 6 months	198	−.24	< 001
9	202	− 13	< 10
12	205	− 13	< 10
18	195	− 02	—
24	202	− 05	—
36	203	08	—

differ significantly from that of the children whose mothers did not go out to work ($\chi^2 = 2.360$) ('long-sleepers' versus 'short-sleepers' cf. above)

Relation of length of sleep to mental development quotient The correlations between the children's total length of sleep and the developmental quotient obtained by Brunet-Lezine's development test at each interview are shown in Table 5 At 36 months the Terman-Merrill intelligence test was used. It will be seen that a weak *negative correlation exists only at 6* months At the other tested age-levels the connection can be neglected.

Day sleep–night sleep Day sleep is here defined as the sleep that occurs after the family and the child have awakened in the morning and up to the time usually between 5 and 7 o clock in the evening when the child goes to sleep for a longer stretch In general, it was easy to apply this definition when the children had reached the age of 6 months. But even after 6 months it seemed in some cases uncertain whether the sleep periods in the afternoon and early evening were to be counted as day or night sleep For example a child who sleeps from 4 to 7 p m but then stays awake for several hours to enter his longest stretch of sleep after say 10 p m was considered to settle for the night at the latter hour On the other hand, in the case of a child who having settled at 6 p.m wakes up for his evening meal at 10 p.m and then goes to sleep again, the child's night sleep was counted as from 6 p.m This problem of definition does not of course affect the total length of sleep discussed in previous sections but will be of significance in the study of changes in the day sleep and the night sleep respectively

Earlier studies [1 2 4 7 19] have shown that the infant's sleep periods during the first few weeks of life are more evenly distributed over the twice-round the-clock period. A distinct day–night rhythm cannot be discerned The change over to a 24-hour pattern with longer night and shorter daytime periods of sleep occurs gradually According to Hellbrügge [8] a typical day–night pattern can be observed at the age of 4 weeks, but *not until the end of the first year of life* can it be considered to be fully developed Because of the irregularities during the first months of life it has proved difficult by the methods used in this study to obtain accurate values from the ages of 1 month and 3 months. For this reason the data reported below refer to the observations at 6 months and subsequent interviews up to 36 months.

Means and standard deviations for the number of hours of day sleep can be seen in Table 3 (page 108) These hours are *distributed among the number of sleep* periods set out in Table 6 (for the ages 6 12 24 and 36 months)

The need of a nap in the daytime seldom disappears suddenly from one day to another The break-off is usually preceded

mental factors. These are: the position of the child in the family dwelling space with special regard to overcrowding the gainful employment of the mothers, and children s separation during some period from the mothers. The χ^2 analyses has been per formed on data from the investigations at 1 2 and 3 years.

The found significant correlations with the tested factors concern first-born chil dren. At 1 year the first-born in this sample are in 99% analogous with only children. Thus, as regards bedtime resistance behaviour this category is the most troublesome ($\chi^2 = 9.07$ d.f 1 $p < .01$) The trend is the same for first-born and only children at the age of 3 years, but the correlation is significant at a lower level (.05 and .02, respectively)

As regards separation from the mother a correlation on the .05 level was obtained at the age of 3 This means that the child who had had experience of a wholly strange environment some time between 2 and 3 years of age (in hospital, in children home or with non-relatives) was more likely to offer resistance at bedtime than were the others. At other ages this relation was not found

No correlation was noted to overcrowd ing, nor to mother s gainful employment at any age levels.

(b) *Evening wakefulness*

Evening wakefulness denotes here that the child wakes up in the evening before the parents bedtime With this definition the length of the evening will of course vary according to the hour at which the particular family usually go to bed. As far as the child is concerned, evening wakeful ness could be included under night waking in the next section, but it will be dealt with separately for the following reasons. Because of the external factors the child would be more likely to wake up before the rest of the family have gone to bed, and if the child wakes in the evening this is generally less disturbing to the family than if it wakes in the night

The number of children waking regu larly in the evening decreases with increasing age (cf Fig. 5) Thus the trend is different from that shown earlier for resistance at bedtime

The statistical correlation between evening wakefulness and sex was tested for significance by the χ^2 technique. At the ages of 2 and 3 years there are no signif icant relations at 1 year the relation is significant at the 05 level, $\chi^2 = 4.47$ At this ge the boys wake in the evening less often than the girls.

Relation between evening wakefulness at

TABLE 9 *Relation between (a) resistance to bedtime preparation at different ages, (b) evening wakefulness at d fferent ages*

		χ^2	p	χ^2	p
9 months versus	12 months	4.81	< .05	12.82	< .001
12	24	4.34	< .05	11.49	< .001
24	36	27 28	< .001	10.03	< .005
12	36	2.81	< 10	4.47	< .05

is weak ($r = -17$ and $r = -16$ respectively significant on the 02 level) At 1 year there was no significant correlation.

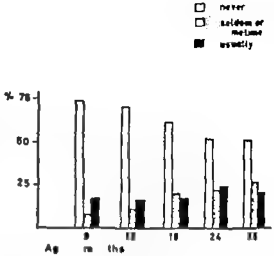

Fig 4 Percentage of children who are resistant at bedtime

III Bedtime Behaviour

Most parents expect the child to sleep from the time it has gone to bed until the family wake up in the morning The disturbances in and deviations from this ideal time-table can be divided into (a) resistance to bedtime preparations (b) evening wakefulness, and (c) night waking These forms of disturbances will here be discussed separately and with a view to their interrelationships.

(a) *Resistance to bedtime preparation*

We are concerned here with a disturbance that often occurs after the child has learnt to walk and shows resistance by refusing to go to bed offering opposition to being undressed, getting up once it has been put to bed, and lying awake grumbling and demanding the family's attention. This disturbance especially in children who cannot yet walk without aid also includes various behaviour in bed which greatly delays sleep Such a conduct lasting for some minutes is of course not recorded as a disturbance unless the mother experiences it as a troublesome situation. The information concerning this bedtime behaviour was collected from the age of 9 months. The grading of the replies will be found in interview form part II column 55 [8]

The percentage of children who go to sleep without disturbances decreases distinctly during the first three years of life The percentage of children who are usually (for grading cf. Fig 4) troublesome at bedtime rises slightly at 24 months and 36 months but the difference from the lower ages is not significant

A significant *sex-difference* as regards resistance at bedtime is obtained only at 3 years. The χ^2 value for the correlation is at 1 year 2 88 at 2 years 1 77 and at 3 years 7 87 The girls show predominance in the resistance group

Relation between resistance to bedtime preparation at different ages The relation between a child's bedtime behaviour at different ages, as expressed in χ^2 values, is shown in Table 9 The values are listed in order of the magnitude of the age-difference

The relationship that exists between bedtime behaviour at different age levels suggests a relative constancy of conduct which is particularly marked on comparison between the later ages, that is, when the child is older

Relation between resistance to bedtime preparation and some environmental factors The resistance behaviour at bedtime has been analysed in relation to some environ

hours but on the other hand, this would have yielded less accurate result with respect to the character of the disturbance. Therefore as regards time, the waking studied here is restrictedly nightly and would be more disturbing to the environment than would wakefulness at other times.

Fig 6 gives an idea of the incidence of night waking at the different age-levels. The data reported here refer only to the disturbances at the time of the interviews with a margin of about 1 week. Thus, the number of children who had sleep disturbances during the intervals between the visits will not influence the result.

The incidence of qualified night waking once or several times every night ranges from 14% to 24% in the age-period from 6 months to 3 years. If the frequency of 3 to 6 night wakings a week is added, the incidence of night waking will range between 23% and 39%. Percentage figures of a similar order has been reported in other studies (5 15). The term sleep disturbance does not necessarily imply that the waking is highly troublesome to the child or its environment although it occurs often in the course of the week. The inconvenience to the family is in most cases considerable however But at some ages there are marked divergencies between the factual incidence of waking and the frequency with which the mothers complain of the situation. This holds true in particular for the conditions at 1 month and at 3 years (cf page 106).

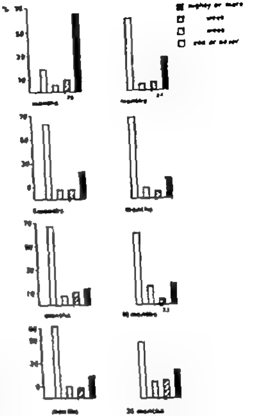

Fig. 6. Incidence of night waking at different ages. Percentage distribution.

In the analyses made to study the relation of night waking to various factors, the group with night disturbances includes unless otherwise stated, children who wake once or several times in the night and those who wake 3 to 6 times a week. Nightly disturbances once or twice a week are excluded.

The first analysis concerned *sex-differences*. The proportions of boys and girls in the night-waking group at 1., 24 and 36 months deviated only slightly from the expected distribution and the analysis gave very low χ^2 values.

Relation between night waking and total length of sleep. As to the children's total length of sleep at 12 months there was a correlation with the night waking, significant at the 5% level. This correlation implies that the children with night disturb-

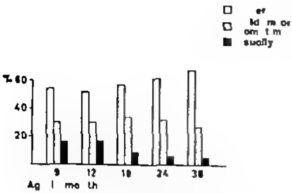

Fig 5. Percentage of children with evening wakefulness.

different ages These values are shown in Table 9 (page 113) listed in order of the magnitude of the age-difference similarly to those for resistant bedtime behaviour It will be seen from this table that for yearlong periods the evening wakefulness seems to be a constant feature in the sleeping pattern of some children.

Relation of evening wakefulness to some environmental factors In the analyses of evening wakefulness largely the same statistical calculations were made as in the case of resistant bedtime behaviour Two probably significant correlations were found. (*a*) Children who had been in hospital, children s homes or with non relatives some time between 2 and 3 years of age were disturbed in a higher degree than children without separation from their mothers ($\chi^2 = 4\ 04$ $p < 05$) No significant relationship was found to separation between 1 or 2 years of age (*b*) Children with separate bedrooms sleep with less disturbances in the evenings than children who had to share their bedrooms with the parents and/or siblings ($\chi^2 = 3\ 86$ $p < 05$ at 1 year and 4 62 $p < 05$ at 3 years of age At 2 years no significant correlation $\chi^2 = 2.51$)

Children of mothers with gainful employment outside the home were awake as often as other children ($\chi^2 = 0\ 03$)

Relation between resistance to bedtime preparation and evening wakefulness To find out whether the children who are troublesome at bedtime are also those who wake in the evening the significance of the correlation between the groups at 1 year and 2 years was tested by the χ^2 technique The correlation was not significant χ^2 values: at 1 year 2 44 at 2 years 0 03

(c) *Night waking*

Night waking is here defined as the interruptions of the child s sleep that occur between the parents bedtime and 6 a m unless caused by the family s early morning habits In order to distinguish between night waking and early (before 6 a m.) waking in the morning the latter was recorded separately In some cases especially in the first year of life it was difficult to decide where to draw the line between early morning wakefulness and night waking Almost without exceptions interruptions of sleep between 5 and 6 a.m were recorded as early morning wakefulness, and those before 4 a.m as night waking An interruption between 4 and 5 a.m was generally referred to the early morning group unless it was quite clear that the waking meant only a momentary break in a stretch of sleep hours. So on some occasions the situation was assessed from case to case the problem being to decide whether the child had broken off its longest stretch of sleep and then began a fresh sleep cycle of a more varying sleep–wakefulness pattern It would of course have been easier to draw the lines strictly at certain

hours but, on the other hand, this would have yielded a less accurate result with respect to the character of the disturbance. Therefore as regards time the waking studied here is restrictedly nightly and would be more disturbing to the environ ment than would wakefulness at other times.

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The incidence of qualified night waking once or several times every night ranges from 14 % to 4 % in the age-period from 6 months to 3 years. If the frequency of 3 to 6 night wakings a week is added, the incidence of night waking will range between 23 % and 30 %. Percentage figures of a similar order has been reported in other studies (5 13). The term sleep disturbance does not necessarily imply that the waking is highly troublesome to the child or its environment, although it occurs often in the course of the week. The inconvenience to the family is in most cases considerable however. But at some ages there are marked divergencies between the factual incidence of waking and the frequency with which the mothers complain of the situation. This holds true, in particular for the conditions at 1 month and at 3 years (cf page 100).

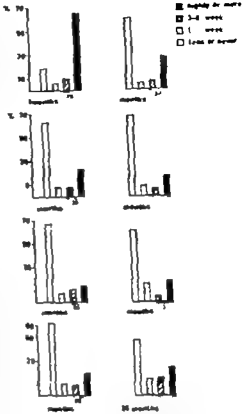

Fig. 6. Incidence of night waking at different ages. Percentage distribution.

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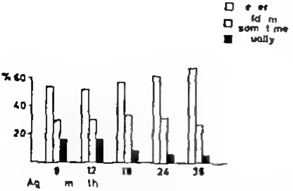

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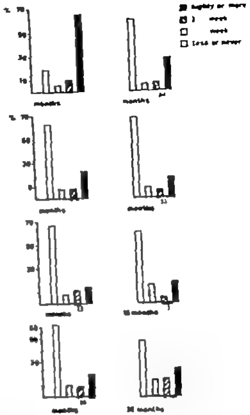

Fig. 6. Incidence of night waking at different ages. Percentage distribution.

The first analysis concerned *sex-d ffer ences* The proportions of boys and girls in the night-waking group at 12, 24, and 36 months deviated only slightly from the expected distribution and the analysis gave very low χ^2 values

Relation between night waking and total length of sleep As to the children s total length of sleep at 12 months there was a correlation with the night waking, signi ficant at the 5 % level. This correlation implies that the children with night disturb-

TABLE 10 *Relation between night waking at different ages*

		n	χ^2	p
3 months versus	9 months	157	12.39	< 001
6	12	160	17 48	< 001
6	24	161	3 6	< 03
6	36	156	4.6	< 05
12	24	167	13.59	< 001
12	36	160	14 97	< 001
24	36	155	6 34	< 02

ances sleep less than others The children were divided by length of sleep into 3 groups in which the frequency of night disturbances was studied (2×3-fold table) The first group comprised all those who slept shorter than the average group the second one was the average group and the third one those who slept longer (cf also Fig 3 page 108) $\chi^2 = 6.37$ d.f $= 2$ $p < 05$

The corresponding χ^2 values for 24 and 36 months were 3 33 d.f $= 2$ and 1 91 d.f $= 2$ *thus no significant correlations.* This difference may indicate that the night wakings at the later ages of 2 and 3 years are often shorter interruptions which do not reduce the number of sleep hours to any great extent

Relation between night waking at different ages of the same child The analyses were made after recording in a fourfold contingency table with those without sleep disturbances in one variable and the night-wakers in the other the correlation between the different ages was tested by the χ^2 technique (table 10)

In analogy with the results for bedtime behaviour and evening wakefulness it seems that for a long time night disturbances also form a recurring feature in the sleep-behaviour pattern of some children

Relation between night waking and evening wakefulness There is a positive correlation of night waking to evening wakefulness at 12 months ($\chi^2 = 6\ 05$ d.f. $=$ 1 $p < 05$) but the correlation is not significant at 24 months ($\chi^2 = 2.68$ d.f $= 1$) Accordingly the children who wake in the evening probably also wake in the night at the age of 1 year

Relation of night waking to some social and environmental factors Neither the family s social class, the child s position in the family overcrowding, separate bed room or the mother being gainfully employed nor the child s temporary separation from the mother show any significant relationships to night waking The analyses were made in fourfold contingency tables, where one variable included unbroken sleep and frequent night waking respectively at 1 *2 or 3 years of age* and the other comprised environmental factors at the same time

Relation of night waking to developmental quotient The correlation between night waking and the Brunet-Lézine quotient was analyzed at *6 9 12 18* and 24 months of age At 36 months Terman Merrill quotient was used Two fairly equal-sized groups with a distinct difference in mental development were compared in one group the quotients were at least ½ standard deviation below and in the other at least equally much above the average

None of the relations is significant although the value at 12 months comes close to showing a probably higher frequency of night waking in the children with a higher development quotient (χ^2 0 02, 1 63 3 79 1.33 0 51 0.24 respectively)

IV Night Disturbances During Long Periods

In the previous section dealing with the interruptions of night sleep the analyses concerned mainly the cross-sectional values and their relationships from relatively frequent interviews. As information about the sleep behaviour in the intervals between the interviews was also collected, a distinction can be made between children who slept permanently without disturbances and those who had spells of waking. The children were divided according to a 5-point scale the division being based on the frequency of night waking from 9 months to 3 years. The extremely good sleepers (group 1) were reported to wake very seldom during this period the estimated total spell of waking being at most weeks. In the group of extremely poor sleepers (group 5) the total spell of night waking in each child amounted at least to 1 year. Between these extremes, the rest of the children are grouped on a rising scale as regards the frequency of night waking. There is, thus, a marked difference in the night's rest between the children who fall into the extreme groups. These groups were then tested in various respects against other variables. The number of children in the different groups is as follows:

Group	*Children*
1 Extremely good sleepers	= 44
Good sleepers	= 40
3 Intermediate group	= 50
4 Poor sleepers	= 25
5 Extremely poor sleepers	= 40

(Insufficient dat on sleep were obtained in 1 case.)

T ble 11 shows the variables tested to est blish any correlations or differences between the extreme groups of children with long-continued sleep disturbances and long-continued unbroken nights.

The two groups of children compared differ greatly with respect to night sleep The children in one group have slept without disturbances almost every night for years, whereas those in the other group have wakened often and over a long period. In many other respects, however there are no dissimilarities Among the tested variables, the dwelling conditions and the time of weaning from the breast are, in fact, the only ones that give a probable significance Overcrowding reduces the possibilities for the child to be protected from light and sound in the surroundings In children who are particularly sensitive or who are light sleepers, these external stimuli associated with overcrowding may be a valid cause for waking or at least, tend to make the parents experience the child's night waking as disturbance and complication. Children at the ages with which we are concerned will usually in one way or other make their presence felt when they wake up.

The relationship to breast-feeding is more difficult to xplain. The weaning period occurs later throughout the group of poor sleepers (see Fig 7) The median age for last breast feed is 3 3 months for the good sleepers and 5 8 months for the poor sleepers. For comparison, it may be mentioned that in the total sample (n = 21?) half the children had had their last breast feed at the age of 4 months.

The relationship between late weaning and more frequent night waking is not revealed by cross-section analyses of the

TABLE II *Relation between persistent bad sleep and a number of environmental variables*

Variable	χ^2		p
Sex girls versus boys	0 696		—
Mother s age (up to 25 versus over 25 years)	0 03		—
Child s successional number at 3 years			
(a) Only child versus others	0.227		—
(b) Second child versus others	0.103		—
(c) Third and subsequent children versus first and second	0.011		—
Child conceived after marriage ceremony versus out of wedlock	1 181		—
Social class at age of 3 years: Graff e I and II versus IV and V	0 081		—
Mother's educational level in child s third year of life (I + II + III versus IV + V)	0.225		—
Mother gainfully employed in child first year of life: never versus others	0 190		—
Dwelling conditions:			
Max. ½ room per person versus others	5 945	(Y tes correction)	< 02
Feeding:			
(a) Night feeds < 3 months versus 3 months and more	.388		—
(b) Weaning from breast			
< 3 months versus > 3 months	4.546		< 05
< 4 > 4	4.354		< 05
< > 7	5 790		< 0*

total sample at the different age levels. χ^2 values are all below significance The reason why a relationship as demonstrated earlier for the more continuous night disturbances failed to appear in the total sample would be that at each age level there are in addition numerous temporary night disturbances that may conceal any associations with various factors in the extreme group of poor sleepers.

For the great majority of children who wake in the night temporarily or habitually at *for instance 12 or 24 months the* duration of breast-feeding is of no significance But in those with more permanent and troublesome sleep disturbances some sort of relationship seems to exist Whether it is causal or explained by coincidences of common factors in the child or the mother remains an open question Gottfarb *et al* [5] who also found a relationship between sleep disturbances and duration of breast feeding suggest that children whose mothers have insufficient milk but are still anxious to feed their babies themselves, would wake from hunger and that waking would thus become habitual

In the present study such a cause might be possible for about *half* of those who *have been defined as extremely poor* sleepers. They meet the criterion of having had sleep disturbances almost uninterruptedly since the period of breast feeding whether the weaning had been late (16 cases) or early (8 cases)

Night waking at 1 month is mostly interpreted as due to hunger and is treated by feeding If the child settles after the feed, hunger is taken to be the cause of the sleep disturbance The parents find either that the night feed comes later each night, until it coincides with the early morning feed, or that suddenly one night the child sleeps through without waking. When, at a later stage of infancy or in the first or second year the unbroken sleep is disturbed again, the causes of the disturbance are not so uniformly interpreted. But up to between 1 and 1½ years however night feeding is the method most usually tried, though without having the same effect as during the first few months of life (cf. page 120) To find out whether there is any relationship between the habit of night feeding at 3 months of age and later night waking at various ages, the statistical correlation was sought by means of χ^2 analyses in the total sample The results are set out in Table 12.

It will be seen that the relation was highly significant at 6 and 9 months, decreased with increasing age and finally disappeared This is readily explained by the fact that children who wake for a

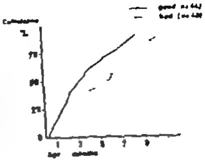

Fig. 7 Age of weaning in good and bad sleepers. —— = good (= 44); —— = bad (= 49).

night feed at 3 months will, to some extent, also do so at 6 9 and 12 months. In so far as night feeding is occasioned by hunger and this night waking is habit-forming the statistical correlation in an earlier phase should not cease to exist. Now the reverse is the case when the child is adjusted to an adequate feeding schedule the established correlations disappear and other causes of night disturbances supervene

In late-weaned children breast-feeding inadequacy might be one cause among others. We do not know if the habit-forming power is stronger when the child has passed 3 months of age. W cannot show it statistically nor exclude this possibility We know however that the infant sucking has emotional qualities as well Therefore we can also look upon night waking in children with breast-feeding of long duration as related to this emotional sphere in one way or another

TABLE 12. *Relation between night feeding at 3 months and night waking at various age levels*

Night feeding/no night feeding at 3 months versus night waking/no night waking.

Age (months)	χ^2	p
6	13 83	001
9	11 35	< .001
12	4.3	< .05
18	1 5	—
24	0 02	—
36	0.03	—

The effect of the treatment methods used In the case of children who have long periods of wakeful nights, the parents have the opportunity of trying various methods for settling. At each interview the mother stated what methods they tried and which of them had been most effective

TABLE 11 *Relation between persistent bad sleep and a number of environmental variables*

Variable	χ^2		P
Sex, girls versus boys	0 696		—
Mother s age (up to 25 versus over 25 years)	0 09		—
Child s successional number at 3 years:			
(a) Only child versus others	0.227		—
(b) Second child versus others	0 10*		—
(c) Third and subsequent children versus first and second	0 011		—
Child conceived after marriage ceremony versus out of wedlock	1 181		—
Social class at age of 3 years: Graffar I and II versus IV and V	0 081		—
Mother s educational level in child third year of life (I + II + III versus IV + V)	0.225		—
Mother gainfully employed in child s first year of life, never versus others	0 190		—
Dwelling conditions:			
Max. ½ room per person versus others	5.945	(Yates correction)	< 02
Feeding:			
(a) Night feeds < 3 months versus 3 months and more	2.288		—
(b) Weaning from breast			
≤ 3 months versus > 3 months	4.546		< 03
≤ 4 versus > 4	4.354		< 03
≤ 7 versus > 7	5.700		< 02

total sample at the different age-levels. χ^2 values are all below significance The reason why a relationship as demonstrated earlier for the more continuous night disturbances failed to appear in the total sample would be that at each age-level there are in addition numerous temporary night disturbances that may conceal any associations with various factors in the extreme group of poor sleepers.

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18	1.2	—
24	0.02	—
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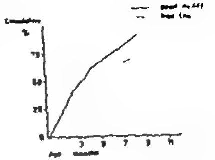

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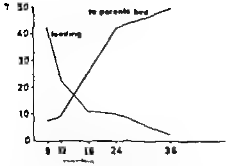

Fig 8. Most effective of methods used at various ages (bad sleepers).

In the extreme group of bad sleepers the results had evidently not been spectacular as the habit of waking in the night had persisted for a long time But on each particular night the waking could be offset with different degrees of success by various methods, and it is this preference for and confidence in a particular method that are expressed in the replies. The answers represent all sorts of methods which mirror the efforts of weary parents to handle the night wakefulness. The methods range from those of punishment (a few cases) to those aimed at making the child feel comfortable and secure The use of drugs is not common. The two methods which are used most commonly but which vary with the age of the child are feeding in the night and letting the child get into the parents' beds No other method alone is used more frequently than any one of these two The variations in the frequency of these methods at different ages will be seen in Fig 8

Summary

The study is part of a prospective longitudinal investigation which comprises 212 children chosen randomly from a Swedish urban community The sleep behaviour of the children which is reported here was followed up to the age of 3 years. Mean values with standard deviations for duration of sleep (total, day sleep and night sleep) at 6 9 12 18 24 and 36 months are presented The length of night sleep increases slightly but because the day sleep decreases much more the 3-year-old will on an average sleep nearly $2\frac{1}{2}$ hours less per 24 hours than will a 6-month-old baby The total length of sleep per 24 hours does not vary with the amount of day light hours. A calculation of correlation also shows that the possibilities to predict the length of sleep at a later stage of the child's life are small. The length of sleep showed no statistical correlation with a great number of tested environmental factors The latter included overcrowding and the mother being gainfully employed.

Analyses were made of various forms of sleep disturbances their frequency at 8 different age-levels and their continuity and associations with various environmental and constitutional factors For yearlong periods resistance to bedtime preparations, evening wakefulness and night waking form a recurrent feature in the sleep-behaviour pattern of some children. The incidence of night waking which at no age is below 23 is highest at 1 month being 75 %. The interruptions of night sleep show no relationship to the tested environmental variables, whereas the disturbances in the evening and in connection with bedtime preparation were found to be related to external stimuli and strange experiences to the child such as separation from the mother

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for just over 2 years and the extreme group of children who had slept without disturbances. Among the tested variables, only marked overcrowding and prolonged breast-feeding were related to a tendency to wakefulness.

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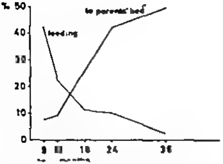

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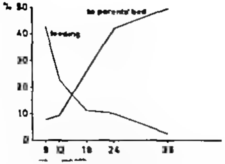

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SYNDROME
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ꞦEPORT OF NINE CASES

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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THE PRADER LABHART-WILLI SYNDROME
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BY HENRY G

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In 1956 Prader, Labhart and Willi (47) in Switzerland first described a syndrome of obesity, small stature, oligophrenia and acromicria (i.e. small hands and feet), regularly preceded by severe amyotonia in infancy. Variable minor degenerative stigmata were also noted in children of both sexes, and the boys had a hypoplastic flat scrotum with inguinal or abdominal retention of testes. The patients had all been extremely limp as newborns, unable to cry or suck, with absent or weak tendon reflexes. They passed their locomotor milestones with delay. About the second year they began to be obese, and delayed growth and mental retardation became noticeable, while the hypotonia and weakness improved and the deep tendon reflexes became stronger. In the males the development of puberty appeared to be delayed and incomplete. The oldest boy developed diabetes mellitus at 17 years; his excretion of gonadotrophin was raised.

Once again in 1956 these Swiss authors, together with Fanconi (48), described the syndrome at the 8th International Congress of Paediatrics. In 1961 Prader and Willi (49) presented an analysis of 14 cases at the 2nd International Congress on Mental Retardation, and the published summary was a little more detailed than the previous abstracts. They added that the mother usually noted diminished fetal movements during the pregnancy and that the average birth weight was less than 3 kg. The later intelligence quotient (I.Q.) was said to be about 40 to 50. Two out of five patients above the age of 1[illegible] years had developed diabetes mellitus, and a third had pre-diabetes at 15 years. In both the established cases the diabetes was stable, without emaciation or acidosis, and thus suggestive of the maturity-onset type of disease. One of the two patients had died of diabetic angiopathy at 28 years. The authors were unable to indicate a definite cause for this syndrome but suggested a genetic defect, probably with a recessive mode of inheritance. There were, however, no known cases of the occurrence of the syndrome in siblings or in more distant relatives.

Again, in 1961, Laurance (38) described six similar cases in boys at the annual meeting of the British Paediatric Association. The patients were chromatin-negative and had normal chromosomes. In the same year the present writer, together with Drs. Ford, Auersperg and Miller (12), published a report concerning a boy who had benign congenital hypotonia with hypogenitalism and had been found to have an extra small chromosome in the G group. The clinical findings in this boy corresponded closely to those of the syndrome described by Prader and his colleagues. The extra small chromosome was later identified as a Y, so that the patient has an XYY karyotype.

In 1962 Gabilan (19) reported four cases in France, and further details of these patients were given by Royer (55) in the following year. The first two of these children were siblings, and the parents of the fourth patient were stated to be consanguineous, hence these cases support the assumption of a recessive genetic defect. However the siblings must be described as atypical in their clinical features, since both had seizures in early infancy, both became obese unusually early (at 8 and 6 months, respectively), both showed excessive sensitivity to intravenous insulin, with hypoglycemia unresponsiveness, and the boy had palpable testes. The fourth patient, a girl who developed diabetes mellitus, had not shown any amyotonia in the neonatal period and thus lacked an important feature of the syndrome. Also in 196[illegible], Zellweger and his colleagues (72) in the United States described a boy with characteristic symptomatology who, in addition, had an abnormal urinary tract. The authors stated that they had observed 10 cases of the syndrome described by Prader and Willi, and that testicular biopsies in a 5-year-old and a 3-year-old patient had shown infantile testes without germinal cells. A chromo-

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somal aberration had been found in only one case, a boy mentioned in a previous paper (71), who had a 14–18 translocation.

In 1963 we summarized our experience with 4 Canadian cases of the condition (13) Clinically in addition to the features described by Prader and his colleagues, these patients presented dental abnormalities, *particularly* enamel defects, and abnormalities of ocular movements.

In 1964 Forssman and Hagberg (18) described a Swedish boy of 10 years with the syndrome who had an I Q of no more than 20 The presence of pre-diabetes was demonstrated by the use of the cortisone-glucose tolerance test (17) The chromosomes in this boy were normal, but the writers drew attention to a report by Bühler *et al* (4) who had described a boy with similar clinical findings and with a karyotype suggestive of a translocation of two autosomes in the 13–15 group In the same year Sánchez Villares *et al* (56) reported a case in Spain. Evans (16) published details of 8 British cases, all boys. In these, gross obesity had developed at a mean age of $2^1/_2$ years. The I.Q varied from 41 to 87 with a mean of 61 Glucose tolerance tests showed impairment in 4 of the 8 patients, and 2 with normal results had deficient glucose tolerance after cortisone. Evans suggested that the patients should be investigated for the presence of an insulin antagonist.

In 1965 two notable cases were reported in France. One, a boy of $13^1/_2$ years, appeared to have mosaicism for trisomy of a D chromosome (group 13–15) (54) The other a boy of 3 years 8 months, had already developed diabetes at the age of 6 months (36) Monnens and Kenis (44) encountered 3 cases in Holland and drew attention to disturbed diurnal variation of the plasma 11 hydroxy-corticosteroid level in 2 of them.

In 1966 Hooft *et al* (29) gave a detailed description of 4 patients in Belgium. Independently of our own observations (13) these authors found a convergent strabismus in all 4 and marked tooth decay in 2 of the children. Sugarman and Boder (61) described the occurrence of the syndrome in an American negro boy

In 1967 Laurance (39) summarized his findings in 9 patients, including two girls. He emphasized the characteristic facies, with prominent forehead and slightly open, fish-like mouth. In one of two muscle biopsies in these cases Dr A. L. Woolf noted that intravital staining with methylene blue showed some finely beaded fibers in the smaller nerve bundles, similar to those seen in Werdnig-Hoffmann's disease, but less numerous. In a third muscle biopsy Dr V Dubowitz found a normal content of glycogen and of several tissue enzymes. The palm and finger prints of 6 boys were examined by Professor P E. Polani who found an *atd* angle exceeding 57 in 2 and a hypothenar loop pattern in 5 whereas these features are present in at most 10 and 15% of the normal population, respectively In another article, Hoefnagel *et al.* (28) reported 4 further American patients. Dubowitz (10) presented ? new British cases one of these had an abnormal chromosome No. 16, which was also present in the mother Juul and Dupont (31) described the oldest known patient with this syndrome, a man aged 43 years, whose endocrine system was investigated in detail

It will thus be seen that about 70 cases of the syndrome had been recorded by the end of 1967 mostly in Europe. The purpose of the present paper is to summarize our own findings in a total of 9 patients and to review the features of the condition.

CASE REPORTS

Case 1

B.M. is the boy already published in 1961. He remains the youngest of 3 children, the mother also had 2 miscarriages. In the family history it is noted that the maternal grandmother has diabetes mellitus and that a maternal uncle failed to take feedings satisfactorily after birth and died at 3 months. The present pregnancy was described as normal except for slight "spotting" at 6 weeks. Labor occurred 10 days after term and ended in a fairly easy breech delivery after less than 3 hours. The baby weighed 2892 g and was limp and blue at birth but responded to resuscitation.

At 6 days, when I first saw him, he was fair-haired and still listless and limp with a whining cry lying curled up with hunched-up shoulders and adducted hips. The palpebral fissures had slight mongoloid slant. The lower jaw was slightly short. The pinnae appeared soft, and the external auditory meatuses were unusually narrow as in Down syndrome. The scrotum was small and empty The infant was generally hypotonic. There was a feeble Moro response, and no stepping reflex was obtained. He sucked poorly No tendon reflexes could be elicited. A weak withdrawal response was demonstrated in the legs.

Subsequently the infant remained so weak and sucked so poorly that his mother gave him formula by spoon from the *ge of 7 /* weeks. However he did smile at

Table 1 *Some features in history and development of 9 patients with Prader–Labhart–Willi syndrome*

Initials (Case No.) Sex (M = male, F = female) Age at last examination (yrs)	B. M. (1) M 8	G. Mc. ( ) M 5	W. W. (3) M 5½	D. M. (4) F 7	J. W. (5) M 5½	R. S. (6) M 20	P. D. (7) M 1	P. F. (8) F 14½	E. H. (9) M 9½
Parity	Youngest of 3	Youngest of 6	Youngest of 3	2nd of 3	Youngest of 5	4th of 5	Youngest of 3	2nd of 5	3rd of 5
Maternal miscarriages	2	3	0 (but pregnancy gap)	0	0 (but pregnancy gap)	?	0	0	1 + 1 stillbirth
Other notable family history	See text	Mother glycosuria and see text	None	See text	See text	See text	None	Sib. anencephalic	Father impaired hearing and see text
Foetal movements in pregnancy	Normal	Diminished	Diminished	Diminished	? Increased	Diminished	Diminished	Normal	Normal
Parental ages at birth of child (yrs) (F = father, M = mother)	F 31 M 34	F 45 M 42	F 39 M 38	F 32, M 25	F 37 M 37	F 33, M 29	F 33, M 36	F 27 M 27	F 38, M 34
Delivery re term	10 days after	1 week before	2 weeks after	5 weeks after	At term	At term	10 days after	4 weeks after	1 month before
Birth weight	6 lb. 6 oz. 2892 g	4 lb. 15 oz. 2240 g	7 lb. 1½ oz. 3218 g	6 lb. 7 oz. 2920 g	8 lb. 9 oz. 3884 g	5 lb. 2268 g	6 lb. 6 oz. 2892 g	6 lb. 8 oz. 2948 g	4 lb. 15 oz. 2240 g
Asphyxia neonatorum	+	Moderate	+	Moderate			Moderate		+
Amyotonia congenita		+			+	+	+	+	+
Age when mastering sitting freely	1½ yrs	ab. 1 yr	10 mos	1 yr	14 mos	?	(Not yet at 1 yr)	13 mos	14 mos
Age when walking freely	3 yrs 3 mos	ab. 2 yrs	ab. 21 mos	2½ yrs	1½ yrs	ab. 2 yrs	—	23 mos	ab. 2 yrs
Age at first word with meaning	14 mos	ab. 1 yr	ab. 10 mos	ab. 15 mos	21 mos	?	—	2 yrs	14 mos
Age when weight significantly raised (+2 SD for height-age)	4 yrs	ab. 2 yrs	2½ yrs	2 yrs 4 mos	ab. 3 yrs	ab. 2 yrs	—	ab. 6 yrs	ab. 7½ yrs
Age at closure of anterior fontanelle	2¼ yrs	ab. 2 yrs	ab. 21 mos	?	18–21 mos	?	—	?	?
Latest D. Q. or I. Q.	ab. 50	ab. 70	S-B 69 at 4 yrs 8 mos	WISC full scale 56	ab. 60	30–40	?	WISC full-scale 53	S-B ab. 30

ab. = about.
S-B = Stanford-Binet.
WISC = Wechsler Intelligence Scale for Children.

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Fig. 4. Case 1. Small penis and scrotum at 2 years 4 months, testes undescended.

thout support at 18 months and to sit up by himself at 2 years 1 month (Fig. 1). He finally walked freely at 3 years 3 months.

His weight at 9 months was only 7250 g and thus just below the third percentile. At 18 months there was little change in the weight, while the length of 74 cm had also become significantly small for his age; only eight teeth had erupted. At 2 years 1 month, the upper canines and second molars had not yet come through. The upper medial incisors showed enamel hypoplasia at their cutting edges (Fig. 2). Since the serum protein-bound iodine level was only 3.4 μg/100 ml and the bone age was greatly retarded, he was then given thyroid therapy at 26 months, and some acceleration of growth may have resulted (Fig. 3). He became significantly obese at 4 years, while the stature remained below the tenth percentile. All the deciduous teeth soon became carious and had to be extracted. The penis remained small, scrotum flat, and the testes undescended (Fig. 4).

Psychometric testing at 31 months indicated a mental age of 25 months on the Merrill-Palmer scale, i.e. at the tenth percentile for his age. On the Vineland Social Maturity Scale his motor achievements at that time attained the equivalent for 20 months, while non-motor items corresponded to those of a mental age of about years. However, his subsequent mental development was slow and at 6 years he obtained an I.Q. of only 51 on the Cattell Infant Intelligence Scale and about 50 on the Peabody Picture Vocabulary Test.

The results of investigations are listed in the previous article and in Tables 3 to 5 and 9, so only the abnormal findings will be mentioned here. X-ray examination showed marked hypoplasia of muscle masses in the arms as well as marked delay in the bone age, and slender and poorly mineralized bones. A muscle biopsy of the right deltoid and quadriceps showed somewhat small muscle fibers, but was otherwise normal. The chromosomal karyotype in tissue culture of fibroblasts from prepuce and muscle demonstrated an extra small chromosome, and later leukocyte culture showed that this extra chromosome was Y (Fig. 5).

At 8 years this boy now attends a special class for retarded children. He remains grossly overweight (49 kg, i.e. twice normal or +8 SD for height-age) despite attempts at reducing diet, physical activation and anorexigenic drugs. He has distension striae over the buttocks. The penis and scrotum remain small and the testes undescended. He still talks mostly in single words or short sentences, with poor articulation. He has over

Table 2. *Physical findings in 9 patients with Prader Labhart Willi syndrome*

Stature below mean for age 6/9
Stature more than 1 SD below mean for age 5/9
Stature more than 2 SD below mean for age 3/9
Obesity after infancy—extremely in 8/9
Head circumference normal (±2 SD for age) or increased 9/9
Anterior fontanelle open after age of 18 months 4/4
Small feet and hands (acromicria) 9/9
Undescended testes and small scrotum in boys 7/7
Amyotonia (benign congenital hypotonia) in infancy 9/9
Early caries 6/7 with enamel hypoplasia in 4/6
Phimosis in boys 4/5
Strabismus 7/9
Pes planus 7/9
Attractive facial features with delicate mouth and fair or auburn hair 4/8
Poor modelling of pinnae 4/9
Short toe nails 4/9
Arched palate 3/9
Bilateral simian creases 2/9 (unilateral in one other)
Clinodactyly 2/9
Mongoloid slant of palpebral fissures 2/9
Brushfield spots on irides 2/9
Narrow external auditory meatus 2/9
Partial syndactyly 1/9
Increased palm creasing 1/9
Bifid uvula 1/9

Fig 1 Case 1 Patient standing with support at 2 / years.

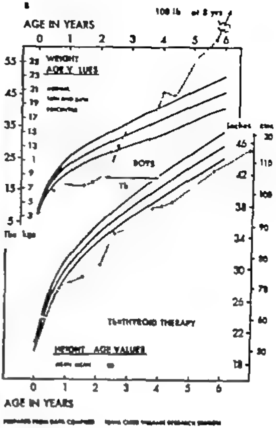

Fig 3 Case 1 Growth chart.

1 month, followed with his eyes at 6 weeks, and turned towards a noise at 2 months. At 4 / months he became active at the sight of a dangling toy. At nearly 6 months he had begun to seize objects. Subsequently he passed most of his locomotor milestones with considerable delay as documented in the previous article and in Table 1. Thus he only became able to remain sitting indefinitely

Fig 2 Case 1. At years 1 month the lower deciduous teeth had all erupted, while the upper canines and second molars had not yet come through. The upper medial incisors show enamel hypoplasia at their cutting edges.

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Strabismus 7/9
Pes planus 7/9
Attractive facial features with delicate mouth and fair or auburn hair 6/8
Poor modelling of pinnae 6/9
Short toe nails 4/9
Arched palate 3/9
Bilateral simian creases 2/9 (unilateral in one other)
Clinodactyly 2/9
Mongoloid slant of palpebral fissures 2/9
Brushfield spots on irides 2/9
Narrow external auditory meatus 2/9
Partial syndactyly 1/9
Increased palm creasing 1/9
Bifid uvula 1/9

Table 3 *Some investigations in 9 patients with Prader–Labhart–Willi syndrome*

N = Normal

Initials (Case No.) Sex (M = male, F = female) Age at last examination (yrs)	B. M (1) M 8	G Mc. (2) M 5	W W (3) M 5½	D M (4) F 7	J W (5) M 5½	R. S (6) M 20	P D (7) M 1	P F (8) F 14½	E. H (9) M 9½
Radiological bone age at hand and wrist	Significantly retarded 5 until last seen	Significantly retarded at 1 yr 9 mos	Retarded significantly in age of 2 yrs, no longer significantly at 4½ yrs	Normal 6 at 9 mos to 5 yrs	Significantly retarded 3 until 3 yrs 8 mos, no longer significantly at 5 yrs 8 mos	Normal at 20 yrs	Significantly retarded at 12½ mos	Normal at 13 yrs	Significantly retarded at 4½ and only just −2 SD at 9½ yrs
EEG	N at 21 mos	—	N at 7 mos and 4½ yrs	—	N at 2½ yrs	—	—	N at 2 mos, low-voltage irreg. fast activity at 13½ yrs	Bisynchronous occipital sp kes at 4½ N at 9½ yrs
Conduction velocity (median nerves)	N	N	N	—	N	—	—	N	N
Electromyogram	N	N	N	—	N	—	—	—	—
Serum cholesterol (mg per 100 ml)	111 at 1 yr 9 mos 148 at 2 yrs 4 mos 186 at 2 yrs 6 mos 143 at 3 yrs 8 mos	—	130 at 7 mos	—	—	100 at 8 yrs 168 at 11 yrs 254 at 20 yrs	—	160 and 180 at 13½ yrs	140 at 9½ yrs
Serum protein-bound iodine (µg per 100 ml)	3 4 at 1 yr 9 mos 4.1 at 2 yrs 6 mos (on thyroid) 5 7 t 3 yrs 8 mos (on thyroid) 4 7 at 4 yrs (off thyroid)	6.6 at 7 mos	4 6 at 7 mos	3.8 at 1 yr 6 mos 5.0 at 1 yr 9 mos (on thyroid) 4.5 t 4 yrs 5 mos (on thyroid)	5.0 at 1 yr	5 6 at 20 yrs	6.1 at 1 yr	—	7 0 at 9½ yrs
Urinary amino-acids (paper chromatography)	N (also indoles)	N	N (also indoles)	N	N	—	N	—	N
Urinary 17-ketosteroids (mg per 24 hrs)	0.66 at 2 yrs 4 mos 2.0 at 3 yrs 8 mos	—	3.32 at 4½ yrs	—	—	4 t 8 yrs 2.7 at 11 yrs 13 6 at 20 yrs	1 5 at 1 yr	7 1 at 13½ yrs	2.0 nd 1.8 9½ yrs

Urinary ketogenic steroids (mg per 24 hrs)	3.08 at 2 yrs 8 mos; 2 at yrs 8 mos		1 at ½ yrs rising to 1.2 at metyrapone test				—	8.1 at 13½ yrs	4.4 and 3.6 at 9½ yrs rising to 14.2 at metyrapone test
Glucose tolerance test (1 g orally per kg body weight)	High N at 5½ yrs		N at 3½ and 4½ yrs	N at 5 above and at 6 yrs 8 mos	N at 3½ yrs	N at 11 high N at 20 yrs	N at 1	Diabetic at 13½	High N at 9½
Cortisone (or prednisone) glucose tolerance test	N at 8	—	Diabetic at 4½ yrs	N at 6 yrs 8 mos	N at 4½ yrs	High N at 20 yrs	High N at 1 yr	—	High N at 9½ yrs
Fasting plasma insulin level (μU/ml)	18.0 2.5	—	1 10	2.5	1 2.5	—	0	0 9	17.5
Synalbumin antagonist	None	—	None	None	Present	—	None	None	—
Buccal smear chromatin	Negative	—	Negative	—	Negative	Negative	—	±4 cells positive	Negative
Chromosomes	XYY	Normal ♂	Long Y and see text	Normal	Normal ♂	—	Normal ♂	Normal ♀	Long Y

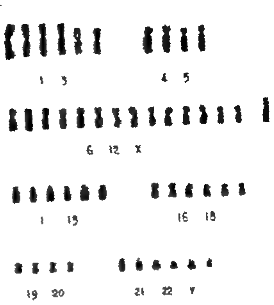

Fig. 5 Case 1. Karyotype showing extra chromosome in group 21 22+Y

action of the inferior oblique muscle of the right eye. He is only mildly hypotonic, but the tendon reflexes are all sluggish (+1). The gait remains cautious and waddling. The behavioral development is indicative of an overall mental age of little more than 4 years according to the Gesell schedule. The bone age is still significantly retarded (4 to 5 years). The cortisone-glucose tolerance test gives no indication of pre-diabetes.

Case 2

G Mc., another boy, is the youngest of 6 children, and the mother also had 3 miscarriages after the birth of the fifth child, who was 14 years old when our patient was born. The boy's siblings are all healthy. A paternal uncle died at 3 to 4 months after incision of an abscess. The mother had some vaginal bleeding at 6 weeks and 6 months and was found to have glycosuria during this pregnancy. She noted little fetal movement. She went into labor spontaneously one week before term and was delivered by Cesarean section because of fetal distress. The infant weighed 2240 g and seemed depressed but was resuscitated. He remained limp and was kept in an incubator receiving formula with the help of a feeder for two weeks. He continued to take feedings slowly and his weight remained over 1 SD below the mean throughout the first year (Fig. 6). He followed with his eyes at 2 months and smiled in response at 2½ months. At 3 months he was re-admitted to hospital with bronchitis and weak cough.

When I first saw him, he was nearly 4 months old and had only just begun to raise his head in the prone position. The palate was moderately arched. The scrotum was small, and the testes were undescended. He had a hampering cry and lay limply on his back but followed

Table 3 *Some investigations in 9 patients with Prader–Labhart–Willi syndrome*

N = Normal

Initials (Case No) Sex (M = male, F = female) Age at last examination (yrs)	B. M. (1) M 8	G Mc. (2) M 5	W W (3) M 5½	D M (4) F 7	J W (5) M 5½	R. S. (6) M 20	P D (7) M 1	P F (8) F 14½	E. H (9) M 9½
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EEG	N at 21 mos	—	N at 7 mos and 4½ yrs	—	N at 2½ yrs	—	—	N at 2 mos, low-voltage irreg. fast activity at 13½ yrs	Bisynchronous occipital spikes at 4½ N at 9½ yrs
Conduction velocity (median nerves)	N	N	N	—	N	—	—	N	N
Electromyogram	N	N	N	—	N	—	—	—	—
Serum cholesterol (mg per 100 ml)	111 at 1 yr 9 mos 148 at 2 yrs 4 mos 186 at 2 yrs 6 mos 143 at 3 yrs 8 mos	—	130 at 7 mos	—	—	100 at 8 yrs 168 at 11 yrs 254 at 20 yrs	—	160 and 180 at 13½ yrs	140 at 9½ yrs
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of about 3 / years, i.e. D.Q. of about 70. He still talked mostly in single words or short sentences. Overaction of both inferior oblique muscles persisted. There was still some general hypotonia, with sluggish tendon reflexes (+1), and the plantar and *Chaddock* responses were equivocal. The gait was wide-based and somewhat waddling. Unfortunately the parents objected to blood sugar investigations.

Case 3

W.W. another boy is the youngest of 3 children. Both parents belong to large sibships, and the family history is non-contributory except that there was gap of 14 years between the birth of the second child and that of our patient. The pregnancy was normal, though the mother commented that the *fetal* movements were weak. Labor occurred about 2 weeks after term and lasted about 4 hours; the *fetal* heart rate was somewhat slow at the second stage, but delivery was soon effected. The placenta was small and appeared infarcted. The birth weight was 3218 g. The infant cried only feebly and appeared cyanosed. On resuscitation his condition improved, but he remained limp during the first month, with little crying or spontaneous movement. He had to be fed by gavage for 3 weeks and then with feeder.

When I first saw him he was 4 / months old and was still unable to raise his head prone. The irides showed Brushfield spots, and both palms had bilateral transverse creases. Otherwise he resembled the boys described previously.

Fig. 8. Case 2. The child has pleasant features like Case 1. Note overaction of inferior oblique muscle of right eye.

Fig. 9. Case 3. Facies at 13 months. Note convergent strabismus and Brushfield spots on irides.

At 7 months he had learned to seize and transfer objects, remained weak and had developed convergent squint (Fig. 9). The bone age was significantly retarded. The conduction velocity in motor fibers of the median nerves was normal, and an electrocardiogram (ECG) and electroencephalogram (EEG) were within normal limits. A muscle biopsy from the right quadriceps showed normal histology. The spinal fluid was normal. Other investigations are listed in Tables 3 to 5 and 7.

This boy gained eight better during the first year than the two previous patients (Fig. 10). At 13 months he was pleasant and auburn-haired, still hypotonic, lying in the frog position (Fig. 11). The scrotum and penis were small and the testes undescended. The feet exhibited short toenails and mild pes planus.

At 2 years he became significantly obese. The convergent squint was corrected surgically; the resected right lateral rectus muscle was normal on section except that it contained some fibrous tissue. Leukocyte culture revealed normal chromosomal karyotype except that both the boy and his father have a long Y chromosome (of about the same length as the group 16–18), and in 19 of 82 cells the long arm of one of the $6-12+X$ chromosomes had a prominent secondary constriction.

At 4 years 7 months this patient was markedly obese (over 8 SD above the mean for his height-age). There much dental caries. The phalanges were poorly modelled (Fig. 12). Distension striae were noted in both groins, and he had "buffalo hump" and prominent buttocks.

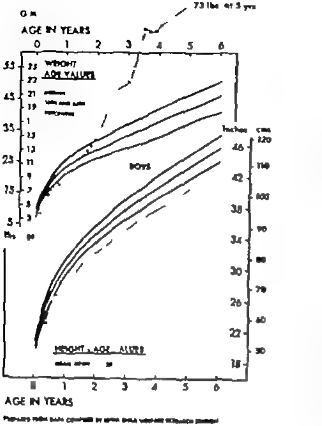

Fig 6. Case – Growth chart. Note marked increase in weight after first year with persistently small stature

with his eyes, sucked quite well and became slightly active at the sight of a dangling toy. Hypotonia and weakness affected trunk and limbs, and the musculature was poorly developed. The tendon reflexes were present but depressed (+1), and the ankle jerks were represented by a mere flicker. Sensation to pinprick appeared intact; the abdominal skin reflexes were present. Skin scratch caused a normal flare response. An *electromyogram* and motor conduction velocity in the left median nerve (36.5 m sec) were normal.

At 7 / months he had learned to seize and transfer objects, but no teeth had erupted as yet and he had an intermittent esotropia as well as *overaction of the inferior* obliques. The head was still unstable in the erect posture. Weakness in the limbs was most marked proximally. X-ray examination of the left arm showed an unusually small muscle mass, while the bony development of hand and wrist was that of a newborn and thus significantly *retarded. Other investigations are listed in Table 3.*

At 21 months this infant was not yet walking freely and had only 4 [illegible] 5 words, but his appetite had improved and the weight had risen above the mean, while the length was nearly 2 SD below the mean for his age (Fig. 6). The anterior fontanelle was still open to a fingertip, head circumference normal. Only the incisor teeth had erupted as yet, and a right upper incisor showed poor enamel on its anterior surface, with early caries. He was beginning to be well-nourished, with small hands and feet (Fig. 7). The joints were generally lax. The squint, *with overacting inferior obliques, was noted again (Fig. 8).* The penis and scrotum remained small, and the prepuce was phimotic. The prostate gland was palpable rectally. Circumcision was *performed,* and fibroblast tissue culture from the prepuce showed a normal male karyotype. Bone development was still that of a newborn.

At about / years this boy became significantly obese. At 5 years his height remained only just above the lower limit of the normal range, whereas the weight of 33.. kg was nearly twice the normal, and no less than 8 SD above the mean for his height-age (Fig. 6). His teeth had not become grossly carious, possibly because fluoride had been administered. He was reported to be somewhat stubborn but usually cheerful and good-natured. On the Gesell schedule he had a mental age

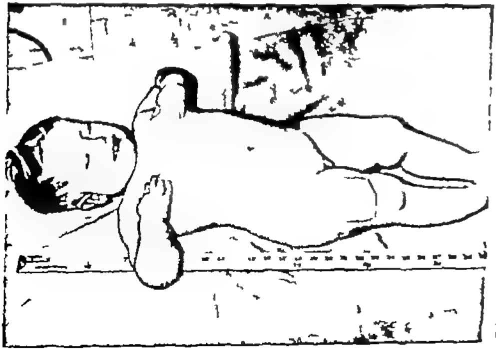

Fig 7. Case – Patient's appearance at .1 months, showing early obesity

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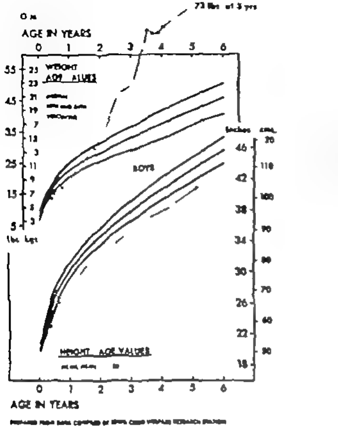

Fig 6. Case 2. Growth chart. Note marked increase in weight after first year with persistently small stature.

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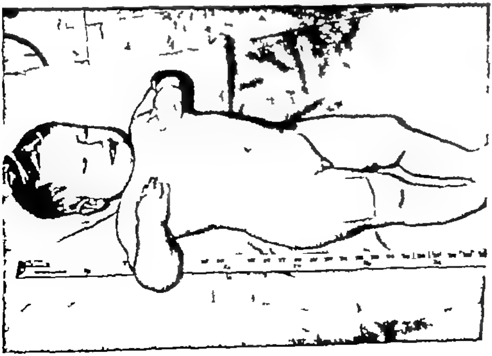

Fig 7. Case 2. Patient's appearance at 1 months, showing early obesity

obese at about 20 years. Otherwise the family history is non-contributory but the father was raised by grandparents and knows little of the family on his side. During the pregnancy with our patient the fetal movements seemed inadequate. Labor lasted about 8 hours, with breech presentation, and during the last half hour the infant passed meconium. Although delivery occurred at least one month after the expected time, she weighed only 2920 g. At birth she had a weak cry and was limp but was placed in an open crib. She remained markedly hypotonic and had to be gavaged for five weeks. "She did not even whimper for three months." Then she gradually became stronger but she only managed to roll around the floor at 1 year and was still unable to remain sitting at that time. Shortly thereafter she learned to say the first words.

At about 1 ½ years she pulled herself to the sitting position. She was then placed on thyroid therapy partly because her serum protein-bound iodine level was only 3.8 µg/100 ml. The weight then rose, and at 2 years 4 months she had become significantly overweight (Fig. 13). Her bone age was normal even before she was given thyroid. The child walked freely at 2 ½ years. She was described as pleasant and cheerful but stubborn.

When I saw her she was nearly 5 years old and was markedly obese, fair-haired and resembled the first 3 patients in her facial features (Fig. 14). She had a lordotic posture (Fig. 15). Her height was just above the lower limit of the normal range, whereas the weight was significantly (+3 SD) in excess of normal even for her actual age. The medial incisors showed enamel defects

Fig. 14. Case 4. Pleasant features and fair hair resemble those of Cases 1 and 2.

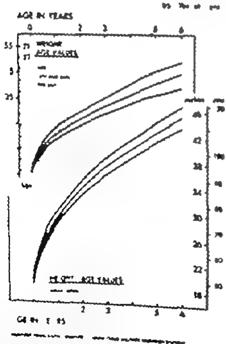

Fig. 13. Case 4. Growth chart, showing rising weight with persistently small stature.

along the incisal edges, and there was also considerable caries. The phalanx was poorly differentiated. Both hands exhibited delicate fingers and transverse palm creases. The feet were somewhat flat, with spoon-shaped toenails. The joints were generally lax. Her speech was satisfactory. The eye movements were normal. There was general moderate hypotonia, with fair power. The tendon reflexes were only doubtfully present in the arms, but the knee and ankle jerks were satisfactory. Coordination was fair but somewhat awkward and shuffling. Her overall behavioral development appeared to be barely at the level of 3 years according to the Gesell schedule so that her D.Q. was about 60. Her chromosomes were normal female.

At nearly 7 years this girl attended a school for retarded children. She weighed 34.8 kg despite attempted dieting. On the Wechsler Intelligence Scale for Children (W.I.S.C.) she had a verbal I.Q. of 71, performance I.Q. 47, full-scale I.Q. 56. On the Goodenough Draw-a-Man Test she obtained an I.Q. score of 70 and on the Vineland Social Maturity Scale S.Q. 80. Two glucose tolerance tests gave divergent results but a cortisone-glucose tolerance test proved normal. Other investigations are listed in Tables 3 to 5.

Case 5

J. W. is the fifth son of healthy parents. He has no sisters, and his brothers are normal, though the second eldest is reported to have been an inactive plump baby

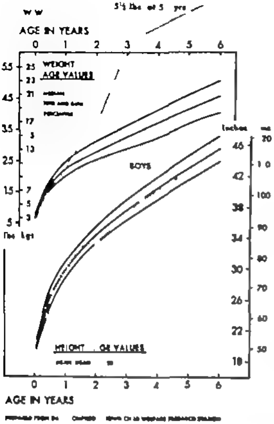

Fig 10 Case 3 Growth chart.

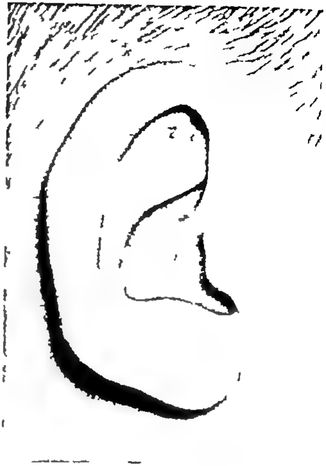

Fig 1 Case 3 Right ear showing poor modelling of pinna.

The appearance of the genitals was unchanged. He had a tendency to echolalia. He was still somewhat hypotonic, with sluggish tendon reflexes (+1) A month later the I.Q. was 69 on the Stanford-Binet Scale, while he scored an I.Q. of 75 on the Goodenough Draw-a-Man test and S.Q. 79 on the Vineland Social Maturity Scale. A glucose tolerance test proved normal but a prednisone-glucose tolerance test gave a significantly different result, with a 2 hour blood sugar value of 179 mg/100 ml and thus indicated a pre-diabetic state (Fig. 27).

Case 4

D M. was the first girl among our patients. She is the second of three children. The parents and siblings are healthy The mother has a maternal half-aunt who is mentally "slow" reached Grade 8 in school and became

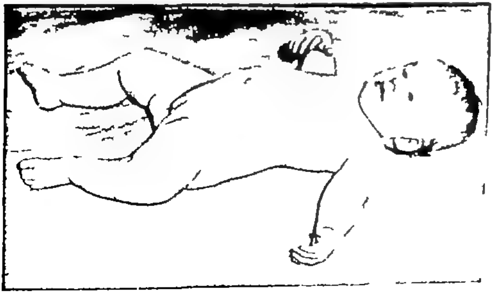

Fig 11 Case 3 Patient lying in frog position at 13 months.

obese at about 20 years. Otherwise the family history is non-contributory but the father was raised by grandparents and knows little of the family on his side. During the pregnancy with our patient the fetal movements seemed inadequate. Labor lasted about 8 hours, with breech presentation, and during the last half hour the infant passed meconium. Although delivery occurred at least one month after the expected time, she weighed only 2720 g. At birth she had a weak cry and was limp but was placed in an open crib. She remained markedly hypotonic and had to be gavaged for five weeks. "She did not even whimper for three months. Then she gradually became stronger but she only managed to roll around the floor at 1 year and was still unable to remain sitting at that time. Shortly thereafter she learned to say the first words.

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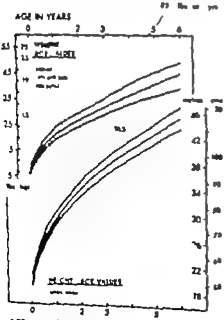

Fig. 13 Case 4. Growth chart, showing rising weight with persistently small stature.

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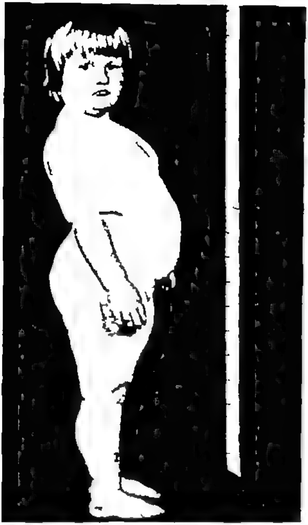

Fig 15 Case 4 The child has a lordotic posture· her obesity is most marked on the trunk and proximal part of limbs.

whose testes only descended after hormone injections at 9 to 10 years. The mother had no miscarriages, but there was a gap of 7 years between the birth of the 4th boy and that of our patient. During this pregnancy the mother had slight vaginal bleeding at 3 months and later thought the fetal movements were *excessive* at times. Labo was *induced medically at term* and proceeded normally lasting about 6 / hours. At birth the infant weighed 3884 g. He obtained an Apgar score of 9 but was immediately noted to be lethargic and floppy From the fifth day he was fed by gavage. Lumbar puncture showed normal spinal fluid. A subcutaneous injection of neostigmine 0.25 mg did not improve his tone. Despite his limpness he turned his eyes to light and sound at three weeks.

When I first saw him he was six weeks old. H lay *limply on his side (Fig 16)* and had a somewhat elon gated head, with slightly short lower jaw and wide fontanelle. The joints were generally lax. The scrotum was small, with a central dimple, and did not contain any testes. The penis was normal in size, with phimotic prepuce. The infant was able to suck and had Moro and asym-metrical tonic neck reflexes as well as plantar grasping, but he was generally hypotonic and unable to raise his head prone, to flex his hips when erect or to make any stepping movements. No rooting response was obtained, and there was pronounced head lag on arm traction. He had intermittent alternating esotropia, and the facial movements were restricted. The weakness of the limbs appeared greatest proximally No tendon reflexes were obtained except flickers of knee jerks. A buccal smear was chromatin-negative Leukocyte culture showed a normal male complement of chromosomes. Electromyo-graphy and measurement of motor conduction velocity in the right median nerve gave normal results. Muscle biopsy from deltoid showed no abnormality and intra-vital staining with methylene blue demonstrated normal motor end plates. Other investigations are listed in Tables 3 and 5 to 7

At 2 / months the infant became able to take formula from a feeder *At 3 months he was beginning to smile.* At 4 months he took bottle feedings. At 4 / months he raised his head prone At 11 / months he began to *crawl and to wave "bye-bye*

At 1 year he weighed 9186 g and had developed such a good appetite that his mother became concerned. He was then a pleasant boy with dark-blood hair and a some-what narrow head (Fig. 17). His length and head circum-ference were normal. Only six incisor teeth had erupted. He had a moderate inspiratory stridor He picked up objects with pincer grasp and rolled over skillfully but was still unable to retain sitting unsupported. There was no Landau postural response, but he did have protective extension of the arms when lowered head-first. The hypotonia was less marked and he no longer slipped through the fingers when held aloft by the axillae but *no tendon reflexes were elicited as yet. An x-ray film of* hand and wrist showed the bone age to be only about 6 months, i.e. significantly retarded.

This boy started to walk freely at 1 / years and said the first words with meaning at 21 months. A years his behavioral development was at a level of about 18 months according to the Gesell schedule, though lower in language development and toilet control. He still had mild alternating esotropia. He tended to hold his mouth open, without excessiv drooling. He was still somewhat hypotonic and *the tendon reflexes remained absent.*

During the following 8 months he gained 4 kg and began to be obese. Many teeth were becoming carious. *He had lax joints, pes planus and mild genu valgum.* At 2 years 8 months the penis measured 4 cm in length, and the testes remained impalpable. There were flickers f knee jerks but no other definite tendon reflexes, though power was now fair

This boy became significantly overweight at about 3 years. Eight months later he had a significantly low *bone age f still only about 2 years. When last seen at* 5 years 8 months he weighed 72 lb (32.7 kg), i nearly +6 SD for his age while the height of 111 cm was slightly below the mean (Fig. 18). The head circumference of 55 / cm had become significantly big for the age (+3 SD). The pinnae were primitive in shape. There was marked truncal obesity with delicate small hands and feet. *The joints remained rather lax. H had bilateral* gen valgum with an intermalleolar distance of 10 cm.

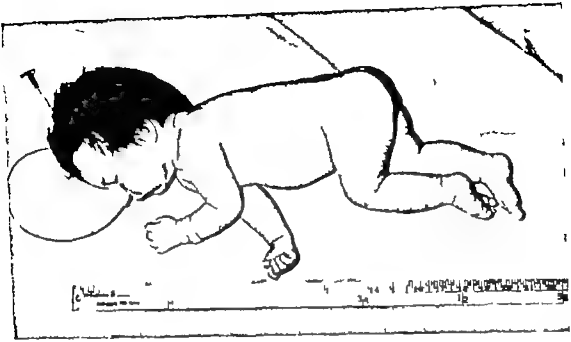

Fig. 16 Case 5 At 6 weeks the infant is lying limply on his side nasogastric tube is used for feeding.

His speech as poorly articulated. He showed some perseveration in his behaviour Gesell testing suggested that he as mildly retarded (D Q about 60). X-ray films of the left arm showed normal-sized muscle mass with excessive subcutaneous fat. The bone age was now about 4 years and thus no longer significantly low Glucose and cortisone-glucose tolerance tests were normal. This boy and brother were shown to have significant amounts of synalbumin antagonist to insulin in their plasma (see Table 6)

Case 6

R S. is the fourth of 5 children His older siblings are all married and have normal children younger brother is healthy and still at home. The father is reported to be healthy farmer The mother has migraine and is described as anxious but genuinely fond of the patient. A maternal aunt had epilepsy but is said to have outgrown it, one of her children is reported to be severely retarded, allegedly from birth injury The pregnancy ith our patient was evidently normal initially but at about 4 months gestation the family home was destroyed by fire and the mother as greatly upset. Subsequently she felt hardly any fetal movements. Labor occurred at term and lasted about 6 hours, anesthetic as used. At birth the infant weighed only 2268 g and was so limp that he was not expected to survive. According to his mother he "did not le for 2 months and just lay silent in his crib without movement He as thin and took feedings very slowly He only regained his birth weight after more than 6 week H testicles were noted to be undescended His mother states that he only gave his first cry after one year and three days. It is said that he could not walk until the age of 2 and did not learn to talk until the age of 6 years. He was good-natured and friendly At years

Fig. 17 Case 5 Facies at 1 year

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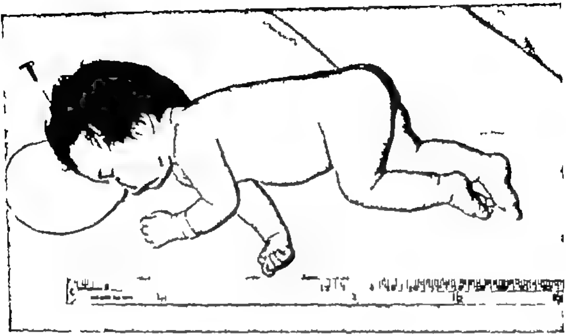

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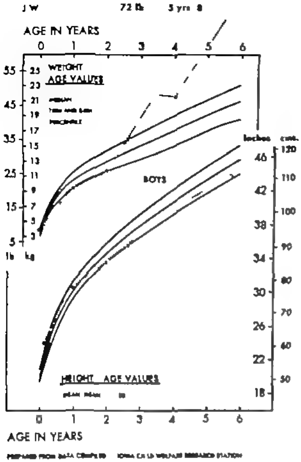


Fig 18. Case 5 Growth chart. *After the first 2 years the weight rises sharply while the height remains low*

he became very fat. After 3 years he had a tremendous appetite and gradually became more difficult to handle.

At 8 years 3 months he weighed 47 6 kg when he was admitted temporarily to the Provincial Mental Hospital. He was described as a very obese fair-haired boy with cheerful expression but inclined to temper tantrums. The penis and scrotum were small, and no testicles were palpable. The Stanford-Binet (Form L) test indicated an I.Q of 40. His highest scores were in comprehension, while the first failures came in recognizing pictorial representations. His enunciation was very poo He walked slowly and with waddling gait. Laboratory investigations were essentially negative (Table 3)

One month later he was transferred to the Woodlands School for the retarded. Despite the use of amphetamine he continued to gain weight. Androgen was also administered. Caries was noted in his deciduous teeth. At 11 years he weighed 91 kg. The head circumference was significantly large (56 / cm, i.e. +3 SD). The penis measured only about 5 cm after years of androgen therapy but acne and the presence of facial, axillary and pubic hair were noted. Glucose and insulin tolerance tests were normal. Androgen therapy was discontinued. At nearly 13 years the boy was discharged home, and 2 years later the family had managed to reduce the weight to 63.5 kg.

At 20 years this patient was re-admitted temporarily to the provincial school for the retarded. He was reported to help on the family farm but had not learned to read or write He had reddish-blond hair and marked truncal obesity (Fig. 19). His height of 160 cm was significantly small, whereas his weight of 100 kg was significantly high for his age and 5 SD above the mean for his height-age. He had Brushfield spots on the irides. The teeth were poorly aligned, with many fillings. The palate was slightly arched. The heart and peripheral pulses were unremarkable, blood pressure 140/80. The penis measured about 7 cm in length and was largely embedded in fat; the testes remained undescended. Pubic hair showed female distribution (Fig. 20) The hands and feet were relatively small and graceful. The right hand showed a transverse palm crease, and both little fingers were slightly incurved. The toenails were small and somewhat curved, and the nails of the little toes were particularly short.

The lad appeared left-handed. He talked mostly in short sentences, with poor articulation, especially for *th-* and *l-*sounds. The eye movements were full, with slight overaction of the right inferior oblique muscle. Hyperopic astigmatism was suspected. Tone and power appeared generally normal and the tendon reflexes wer all present symmetrically (+ ?). Coordination was only fair and he was unable to hop on either foot but did perform tandem gait.

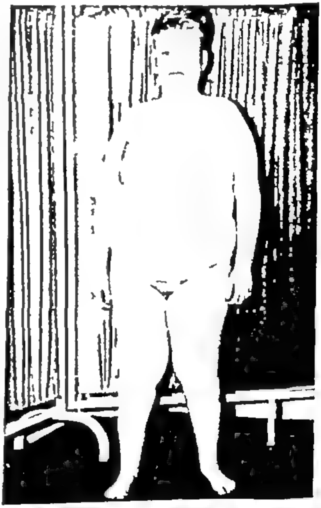


Fig 19 Case 6. At 20 years the obesity affects chiefly the trunk and thighs.

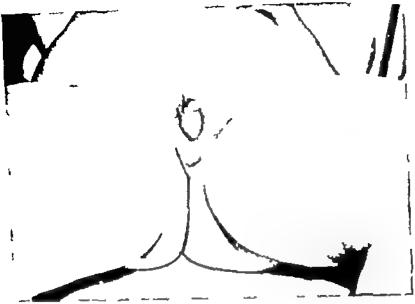


Fig. 20. Case 6. External genitalia at 20 years. The penis is small; the testes are undescended; scanty pubic hair has female distribution.

Psychometric assessment demonstrated particular intellectual dysfunction in visual-perceptual abilities. In his attempts to draw man, or to reproduce digit symbols in the Bender Gestalt test, the patient showed that his ability to reproduce forms as only at the level of 4 to 5 years. His oral verbal abilities were relatively highly developed, with verbal I.Q. of 46 on the Wechsler Adult Intelligence Scale. His social abilities seemed to make the most of his intellectual potential and were rated as S.Q. 32 on the Vineland Social Maturity Scale.

Glucose and cortisone-glucose tolerance tests showed high curves within normal limits. X-ray examination of elbows and knees showed normal skeletal maturity. The urinary 17-ketosteroids ere 13.6 mg and urinary FSH between 6 and 16 mouse units per 24 hours and thus within the normal range.

Case 7

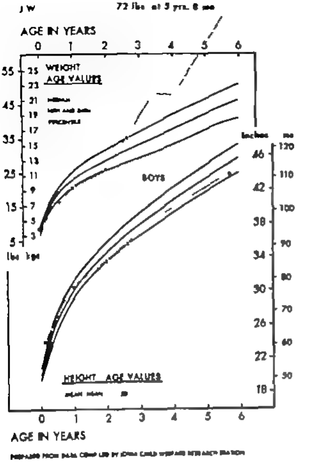
P.D. was an infant of 1 year, the third child in his family. The parents and siblings were healthy. The pregnancy as normal, but the baby did not seem as active as the others had been. Two weeks before delivery there appeared to be breech presentation, but the infant turned spontaneously. Labor occurred normally ten days after term; the birth weight was 2992 g. The infant had very weak cry and had to be tube-fed. The mother, registered nurse, took him home after one week and continued gavaging for 2 months. He then began to suck more strongly, but did not move much and perspired easily. He smiled at 4 weeks, but did not move his hands to his mouth until the age of 6 weeks. At 6 months he began to raise his head prone, and at 10 months he began to roll over. The first teeth erupted at 11 / months.

At 1 year he was still unable to remain sitting or to say any words. He lay limply in the frog position and had pleasant but dull facial features and dark-blond hair (Fig. 21). His length was normal (79 cm), weight 9270 g. Acromicria was noted, with tapering of the distal finger phalanges and small toenails. The dental enamel was hypoplastic. The testes were undescended, prepuce phimotic. The eye movements appeared normal. There was marked general hypotonia, and the tendon reflexes were barely obtainable. X-ray examination showed slender long bones, ith bone age of only 7 months at the hand and wrist. The chromosomal karyotype proved normal. Glucose and hydrocortisone-glucose tolerance tests gave notably divergent curves, but the latter curve was not distinctly diabetic. The results of other investigations are listed in Table 3.

Case 8

P.F., the second girl in this series, is the second of 5 children in her family. The mother first pregnancy had ended in the birth of an anencephalic monster. Otherwise the family history was non-contributory apart from allergies, including asthma. During this second pregnancy the mother had three episodes of slight bleeding during the first trimester. The fetal movements appeared normal. Delivery occurred normally about 4 weeks after term; the birth weight was 2948 g. The infant wa very weak and barely able to take breast feedings. She was discharged home after one week. A week later she was re admitted to hospital after two cyanotic episodes, and her eyes were found to be turned in. She was then markedly listless and hypotonic and kept in an oxygen tent. At 6 weeks neurosurgeon performed pneumoencephalogram, hich revealed only moderate dilatation of the 3rd and lateral ventricles. A neurologist made diagnosis of amyotonia congenita. At 2 / months pilonidal cyst was removed.

Subsequently she only learned to remain sitting at 13 months and walked freely at 23 months. At 14 months she was again seen in neurological consultation and was



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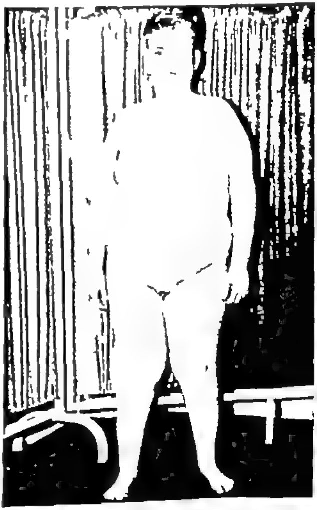

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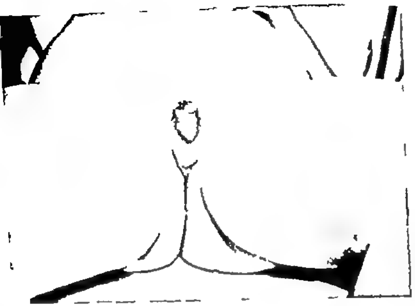

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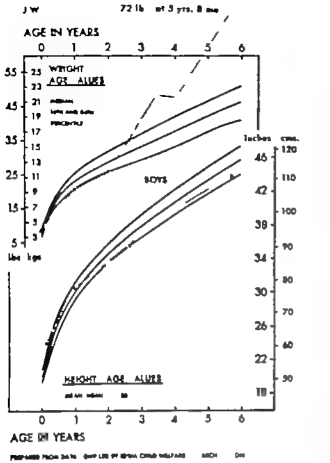

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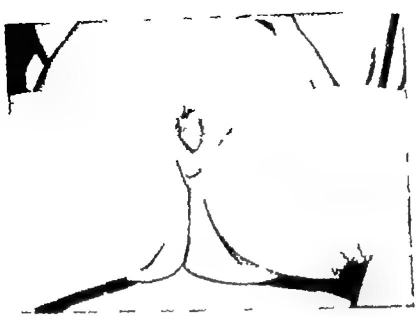

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At 1 year he was still unable to remain sitting or to say any words. He lay largely in the frog position and had pleasant but still facial features and dark-blond hair (Fig. 21). His length was normal (79 cm), weight 9370 g. Acromicria was noted, with tapering of the distal finger phalanges and small toenails. The dental enamel was hypoplastic. The testes were undescended, prepuce phimotic. The eye movements appeared normal. There was marked general hypotonia, and the tendon reflexes were barely obtainable. X-ray examination showed slender long bones, with a bone age of only 7 months at the hand and wrist. The chromosomal karyotype proved normal. Glucose and hydrocortisone-glucose tolerance tests gave notably divergent curves, but the latter curve was not distinctly diabetic. The results of other investigations are listed in Table 3.

Case 8

P.F., the second girl in this series, is the second of 5 children in her family. The mother's first pregnancy had ended in the birth of an anencephalic monster. Otherwise the family history was non-contributory apart from allergies, including asthma. During the second pregnancy the mother had three episodes of slight bleeding during the first trimester. The fetal movements appeared normal. Delivery occurred normally about 4 weeks after term; the birth weight was 2948 g. The infant was very weak and barely able to take breast feedings. She was discharged home after one week. A week later she was readmitted to hospital after two cyanotic episodes, and her eyes were found to be turned in. She was then markedly listless and hypotonic and kept in an oxygen tent. At 6 weeks a neurosurgeon performed a pneumoencephalogram, which revealed only moderate dilatation of the 3rd and lateral ventricles. A neurologist made a diagnosis of amyotonia congenita. At 2 1/2 months a pilonidal cyst was removed.

Subsequently she only learned to remain sitting at 13 months and walked freely at 23 months. At 14 months she was again seen in neurological consultation and was

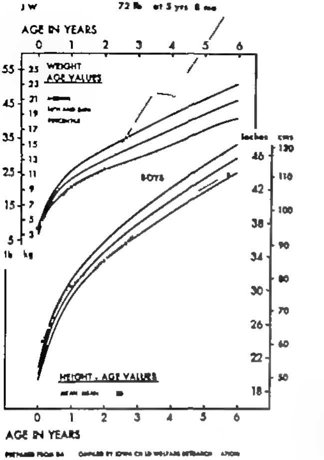


Fig 18. Case 5 Growth chart. After the first 2 years the weight rises sharply while the height remains low

he became very fat. After 3 years he had a tremendous appetite and gradually became more difficult to handle.

At 8 years 3 months he weighed 47.6 kg when he was admitted temporarily to the Provincial Mental Hospital. He was described as a very obese fair-haired boy with cheerful expression but inclined to temper tantrums. The penis and scrotum were small, and no testicles were palpable. The Stanford-Binet (Form L) test indicated an I.Q. of 40. His highest scores were in comprehension, while the first failures came in recognizing pictorial representations. His enunciation was very poor. He walked slowly and with waddling gait. Laboratory investigations were essentially negative (Table 3)

One month later he was transferred to the Woodlands School for the retarded. Despite the use of amphetamine he continued to gain weight. Androgen was also administered. Caries was noted in his deciduous teeth. At 11 years he weighed 91 kg. The head circumference was significantly large (56 / cm, i.e. +3 SD) The penis measured only about 5 cm after 2 years of androgen therapy but acne and the presence of facial, axillary and pubic hair were noted. Glucose and insulin tolerance tests were normal. Androgen therapy was discontinued. At nearly 13 years the boy was discharged home, and _ years later the family had managed to reduce the weight to 63.5 kg.

At 20 years this patient was re-admitted temporarily to the provincial school for the retarded. He was reported to help on the family farm but had not learned to read or write. He had reddish-blond hair and marked truncal obesity (Fig. 19). His height of 160 cm was significantly small, whereas his weight of 100 kg was significantly high for his age and 3 SD above the mean for his height-age. He had Brushfield spots on the irides. The teeth were poorly aligned, with many fillings. The palate was slightly arched. The heart and peripheral pulses were unremarkable, blood pressure 140/80. The penis measured about 7 cm in length and was largely embedded in fat; the testes remained undescended. Pubic hair showed female distribution (Fig. 20). The hands and feet were relatively small and graceful. The right hand showed a transverse palm crease and both little fingers were slightly incurved. The toenails were small and somewhat curved, and the nails of the little toes were particularly short.

The lad appeared left-handed. He talked mostly in short sentences, with poor articulation, especially for *th*- and *l*-sounds. The eye movements were full, with slight overaction of the right inferior oblique muscle. Hyperopic astigmatism was suspected. Tone and power appeared generally normal and the tendon reflexes were all present symmetrically (+). Coordination was only fair and he was unable to hop on either foot but did perform tandem gait.

Fig 19 Case 6. At 20 years the obesity affects chiefly the trunk and thighs.

and appeared small and fibrotic. Two and one-half hours after birth pediatrician found the baby limp and almost motionless, without Moro response or palmar grasp. A blood smear showed plentiful platelets. With tube feedings and incubator care the infant's condition improved only slowly. He developed bilateral cephalhematomata. Three weeks after birth he began to gain weight, and the Moro and palmar grasp responses could be elicited. On discharge home at 7 weeks he still "just lay" and was difficult to feed.

Subsequently he only remained sitting and said the first words at 14 months. The mother said his teeth "looked beautiful, white and even, but quickly decayed." She appears to have rejected this boy emotionally perhaps because she had been told initially that he was brain-damaged and might not survive. At 3 years he was recommended for admission to the provincial residential school for the retarded, since the mother became increasingly nervous. She complained that he seemed hungry and cried all night but never gained. At 4 years he was admitted temporarily to the residential school. He was then significantly small (89 cm, i.e. minus over 4 SD) and

Fig. 22 Case 9 Patient at 9 years, showing obesity of trunk and thighs, significantly small stature, mild genu valgum and underdeveloped genitalia.

Fig. — Case 8 Patient at 13 years, showing obesity of trunk and thighs, significantly small stature, mild genu valgum, and distension striae on lower abdomen.

weighed 15.9 kg. The head circumference was normal. Numerous bruises were noted. His teeth were carious. He had left esotropia and flat-footed, broad-based gait. The bone age was only 2 years (5 SD). An EEG showed activity at 7–9 cycles per second, with considerable hypsynchronous spike activity particularly in the occipital leads.

When he was discharged home it was recommended that he should be placed in foster family but this was not accomplished until he was 7 years old. According to the foster mother he only weighed 15 kg at that time and was unable to talk in sentences. Under her affectionate care he gained no less than 50 lb (22.7 kg) in years. At 8 he was considered to have Stanford-Binet I.Q. of about 30.

When seen at 9 years he presented as dull and obese boy with somewhat pigmented skin suggestive of partly American-Indian origin (Fig. 22). His height of 118 cm was nearly 4 SD below the mean for white boys, while his weight of 40 kg was 6 SD above the mean for

Fig 21 Case 7 At 1 year the boy lies limply has pleasant features and dark-blond hair

considered alert and interested, with improving tone and power She said the first words with meaning at about years. She also developed marked caries, and all the deciduous incisors and canines were removed at 3 years. Subsequently she began to have asthmatic attacks.

At 4 years she weighed only 12.2 kg, but by the age of 6 she was becoming significantly obese and weighed 22.2 kg. At that time she was noted to be clumsy and rather passive her articulation was poor and she tired easily An alternating strabismus was evident. She was still somewhat hypotonic, unable to hop and awkward in attempting to run. Her gait was waddling. The plantar responses were equivocal. At a Child Guidance Clinic she was assessed as having a mental age of 4 years 11 months at a chronological age of 6 years 2 months. She was kept in kindergarten for an extra year and when she started school at 6 years 9 months she was found to be unready and had to repeat Grade 1 After that she attended special classes. At 12 years a psychometric assessment showed her to have a full scale I.Q of 56 on the W.I.S.C. (verbal scale 65 performance 54) On the Peabody Picture Vocabulary Test she attained an I.Q of 66, whereas she only received a minimal I Q score of 46 on the Draw-a-Man test.

When seen at 13 / years she was a pleasant, obese girl with somewhat dull features, brown hair bluish-grey irides and small hands and feet. She was significantly small for her age (142 cm, i.e −3 SD) but weighed 65.4 kg, which was 4 SD above the mean for her height age. The permanent teeth showed moderat caries. The palate was somewhat narrow and arched. The pinnae were poorly modelled. The menarche had not yet occurred but she had moderate mammary development, pubic and axillary hair (Fig. 22). The fat was chiefly deposited on the trunk and proximal part of the limbs, and pinkish-mauve distension striae were noted on the breasts and lower abdomen and over the buttocks. She also had mild genu valgum, xcessive lumbar lordosis, lax joints and flat feet. There was mild left esotropia. She still exhibited moderate generalized hypotonia with fair power and sluggish tendon reflexes. Choreiform mo ements were observed in the outstretched hands The presence of general clumsiness and poor hopping and of equivocal plantar and Chaddock responses was confirmed.

The oral glucose tolerance test (1 75 g per kg body weight) showed a diabetic curve (Fig. 26), while an insulin sensitivity test proved normal. In an insulin-glucose tolerance test, using 1 g of glucose per kg body weight, a diabetic response was noted again. The EEG showed low voltage irregular fast activity in all head regions, without focal or epileptiform abnormality hyperventilation produced rhythmic 9 to 11 per second activity in both posterior head regions in addition to some intermediate slow activity The buccal smear showed chromatin-positive cells. The chromosomal karyotype was normal female. The remaining i vestigations are listed in Tables 3 4 5 and 7

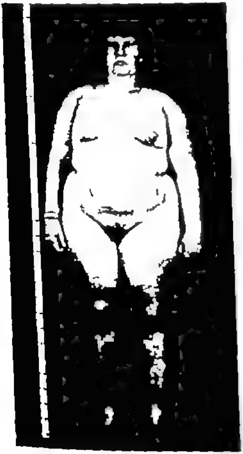
Case 9

E.H. is the 3rd of 5 children, and the mother also had a miscarriage and a stillbirth. The siblings are healthy The father and paternal grandfather developed impaired hearing after the age of about 30 years. The father and mother are otherwise healthy though the latter describes herself as nervous. A maternal uncle is reported to be very small person he is the only survivor of twins, the othe having died malformed at birth. The pregnancy with our patient was uneventful, and fetal movements were felt normally However the membranes ruptured spontaneously a month before term, and the infant was born the same day after labor lasting 6 hours. He weighed only 2240 g and wa cyanosed and slow to breathe. H also showed multiple petechiae. The scrotum was small and empty The placenta had to be removed manually

and appeared small and fibrotic. Two and one-half hours after birth a pediatrician found the baby limp and almost motionless, without Moro response or palmar grasp. A blood smear showed plentiful platelets. With tube feedings and incubator care the infant's condition improved only slowly. He developed bilateral cephalhematomata. Three weeks after birth he began to gain weight, and the Moro and palmar grasp responses could be elicited. On discharge home at 7 weeks he still "just lay" and was difficult to feed.

Subsequently he only remained sitting and said the first words at 14 months. The mother said his teeth "looked beautiful, like and even, but quickly decayed" She appears to have rejected this boy emotionally perhaps because she had been told bluntly that he was brain-damaged and might not survive. At 3 years he was recommended for admission to the provincial residential school for the retarded, since the mother became increasingly nervous. She complained that he seemed hungry and cried all night but never gained. At 4 years he was admitted temporarily to the residential school. He was then significantly small (89 cm, i.e. minus over 4 SD) and

Fig. 23. Case 9. Patient at 9 / years, showing obesity of trunk and thighs, significantly small stature, mild genu valgum and underdeveloped genitalia.



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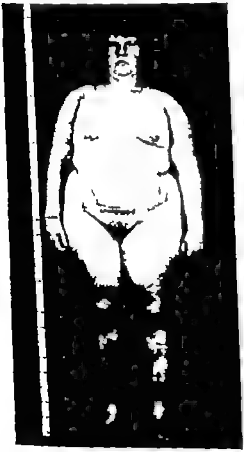

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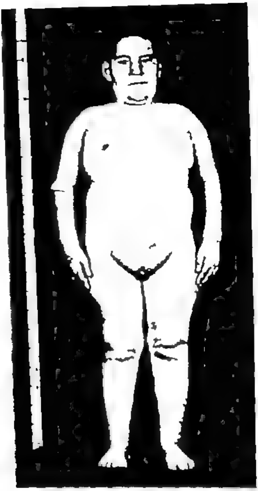

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Fig 24 Case 9 Facies at 9 / years, with mild left esotropia. The skin is somewhat pigmented, hair brown.

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A further EEG now showed no definite abnormality The bone age at hand and wrist was nearly 8 years and thus just significantly low while skull x-rays showed no abnormality The buccal smear was chromatin-negative. The chromosomal karyotype was normal except for a "long Y" as in Case 3 The 4-hour urinary excretion f 17-ketogenic steroids rose from 4 4 and 3.6 mg to 14.2 mg after administration of 2500 mg f metyrapone in divided doses over 24 hours. Glucose and cortisone-glucose tolerance tests both gave somewhat high curves, but neither were definitely indicative of diabetes by the criteria of Fajans and Conn (17) A blood count showed a hemoglobin concentration of only 11 g/100 ml, with moderate anisocytosis, and the serum iron level was 53 μg/100 ml, with a total iron-binding capacity of 446 μg/100 ml, giving a percent saturation of only 12% Other investigations are listed in Tables 3, 4 5 and 7

ANALYSIS OF CLINICAL FEATURES

Sex and age

Seven of our 9 patients are males. This male predominance corresponds to that in other series, but does not necessarily imply that the syndrome is commoner in boys, since it may be merely a reflection of the fact that the hypogenitalism is a more obvious diagnostic feature in males. The ages of our patients vary from infancy to 20 years, and it has been of interest to follow the progess of 4 children (Cases 1 2, 3 and 5) from shortly after birth for 5 to 8 years.

Family history

In these 9 patients the parents are mostly healthy None of them is consanguineous. One mother had glycosuria during pregnancy and one father (and the paternal grandfather) developed impaired hearing after the age of 30 years. Of 8 mothers, concerning whom the information was available, 3 had had 5 2 and 1 miscarriages, respectively and the third had also had a stillbirth (see Table 1). Another of these 8 mothers (Case 8) had given birth to an anencephalic monster prior to the pregnancy with our patient. Two others of this group of mothers (Cases 3 and 5) had gaps of 14 and 17 years, respectively between the previous pregnancy and that with our patient.

Apart from the mother with glycosuria, there is an instance where the maternal grandmother was a diabetic; the other children have no family history of diabetes. Nor is obesity a feature in these families merely one boy has a plump elder brother whose testes only came down after hormone treatment. Mental retardation is reported only in more distant relatives thus the male adult (Case 6) has an epileptic maternal aunt with a retarded child and in Case 4 the mother has a maternal half aunt who is described as mentally slow

A maternal uncle of Case 1 is reported to have taken feedings poorly after birth and to have died at 3 months, but the nature of his disease is obscure A paternal uncle of Case 2 died at 3–4 months after incision of an abscess. A maternal uncle of Case 9 also died in infancy probably owing to congenital malformations.

Parental age

The average age of the fathers at the time of the child's birth was 35 (range 27 to 45) and that of the mothers 33 [illegible] (range 25 to 42) years. The mean maternal age of all live births in the Province of British Columbia in 1955–60 was only 27.0 years, and the mean maternal age of 33.6 years in our series thus would appear to be distinctly higher and also very close to the mean maternal age at the birth of mongoloid children in British Columbia, which was 33.7 years in 1955–60 (52). However, this finding is divergent from that in other series of the Prader–Labhart–Willi (PLW) syndrome. From data kindly supplied by Professor C. Hooft (Gent, Belgium), Dr P. R. Evans (London, England), Dr B. Laurence (Derby, England) and Dr D. Hoefnagel (Hanover, N. H., U.S.A.) the mean paternal age of 18 other patients is calculated as 29.2 (range [illegible] to 40) and the mean maternal age as 27.1 (range 20 to 34) years, and thus both appear to be within the normal range. This discrepancy from our own finding is unexplained. If the parental ages of our 9 patients are added to those of the other 18 cases, we obtain a mean paternal age of 31.1 years and a mean maternal age of 29.3 years for the total 27 patients. As might be expected the mean birth order in our cases is also somewhat high, namely 3.7, as contrasted to 2.3 in Evans' (16) series.

Pregnancy and delivery

The pregnancy was usually unremarkable, though 4 of the 9 mothers had slight vaginal bleeding in the first trimester. In 5 cases the mother considered the fetal movements to be less than normal (Tables 1 and 2), but in one case the mother actually thought that the movements were excessive at times. Two babies (Cases 1 and 4) were born by breech presentation, while a third underwent spontaneous cephalic version prior to delivery (Case 7). One of the babies with breech presentation (Case 4) and two of the others (Cases 2 and 3) showed signs of fetal distress during labor and in Case 2 this led to Cesarean section. Of the 9 infants 4 showed marked asphyxia neonatorum, and another 3 were moderately affected. All these were resuscitated promptly and then breathed quite well, but remained limp. In at least 2 cases (No. 3 and 9) the placenta was noted to be infarcted or fibrotic. The mean birth weight was 2834 g and thus less than 3000 g, as noted by Prader and Willi (49), even though 7 of our 9 patients were born at or after term (see Table 1).

Physical findings

These are listed in Table 2. It will be noted that amyotonia, i.e. congenital hypotonia without evidence of a primary lesion in the lower motor neurone or muscle, was a universal finding in these patients during infancy. Similarly all children had acromicria, though this may be hard to determine with certainty in infancy, and all the boys had undescended testes and a small scrotum. Ultimately all the children also became obese and significantly overweight, but this usually happened after infancy (see Table 1). The mean weight at the age of 3 years was $5^1/_2$ SD above the mean for the height-age. The fat was distributed chiefly on the trunk and proximal part of the limbs.

With the exception of Case 7 (the infant of 1 year) all the children were below average in stature, but only 3 were smaller than -2 SD (more than 2 SD below the mean for their age). The head circumference was usually normal (mean for age ± 2 SD), in 2 patients (Case 5 and 6) it was just significantly large ($+2$ to 3 SD). In the 4 cases in which the time of closure of the anterior fontanelle was known, it was delayed beyond the age of 18 months. Dentition also tended to be delayed. Caries was usually marked in the deciduous teeth, and in 4 of 6 children it appeared to supervene on enamel hypoplasia. One boy (Case 2) who had received fluoride supplement orally did not develop caries like the others, but in another case (No. 5) the administration of fluoride did not prevent the tooth decay.

The younger children had somewhat characteristic, attractive facial features with a delicate mouth, high forehead, blue eyes and fair or auburn hair (see Cases 1 to 5 and 7). Later the features may become coarse and the hair may darken.

Phimosis was present in 4 of 5 boys who had not been circumcised. The penis did not usually appear significantly small in the first year of life, wheras the scrotum was distinctly small (and empty) even at birth. Later the penile size appeared subnormal, even if allowance was made for the suprapubic fat. The prostate gland was palpable rectally.

With regard to the hypotonia it may be noted that the tendon reflexes were initially absent in

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Pregnancy and delivery

The pregnancy was usually unremarkable, though 4 of the 9 mothers had slight vaginal bleeding in the first trimester In 5 cases the mother considered the fetal movements to be less than normal (Tables 1 and 2), but in one case the mother actually thought that the movements were excessive at times. Two babies (Cases 1 and 4) were born by breech presentation, while a third under went spontaneous cephalic version prior to delivery (Case 7). One of the babies with breech presentation (Case 4) and two of the others (Cases 2 and 3) showed signs of fetal distress during labor and in Case 2 this led to Cesarean section. Of the 9 infants 4 showed marked asphyxia neonatorum, and another 3 were moderately affected. All these were resuscitated promptly and then breathed quite well, but remained limp. In at least 2 cases (No. 3 and 9) the placenta was noted to be infarcted or fibrotic. The mean birth weight was 834 g and thus less than 3000 g, as noted by Prader and Willi (49) even though 7 of our 9 patients were born at or after term (see Table 1).

Physical findings

These are listed in Table _. It will be noted that amyotonia i.e. congenital hypotonia without evidence of a primary lesion in the lower motor neurone or muscle, was a universal finding in these patients during infancy Similarly all children had acromicria, though this may be hard to determine with certainty in infancy and all the boys had undescended testes and a small scrotum. Ultimately all the children also became obese and significantly overweight, but this usually happened after infancy (see Table 1). The mean weight at the age of 3 years was $5^1/_2$ SD above the mean for the height-age The fat was distributed chiefly on the trunk and proximal part of the limbs.

With the exception of Case 7 (the infant of 1 year) all the children were below average in stature, but only 3 were smaller than −2 SC (more than 2 SD below the mean for their age). The head circumference was usually normal (mean for age + SD) in 2 patients (Case 5 and 6) it was just significantly large (+2 to 3 SD). In the 4 cases in which the time of closure of the anterior fontanelle was known, it was delayed beyond the age of 18 months. Dentition also tended to be delayed. Caries was usually marked in the deciduous teeth, and in 4 of 6 children it appeared to supervene on enamel hypoplasia. One boy (Case 2) who had received fluoride supplement orally did not develop caries like the others, but in another case (No. 5) the administration of fluoride did not prevent the tooth decay

The younger children had somewhat characteristic, attractive facial features with a delicate mouth, high forehead, blue eyes and fair or auburn hair (see Cases 1 to 5 and 7). Later the features may become coarse and the hair may darken.

Phimosis was present in 4 of 5 boys who had not been circumcised. The penis did not usually appear significantly small in the first year of life, wheras the scrotum was distinctly small (and empty) even at birth. Later the penile size appeared subnormal, even if allowance was made for the suprapubic fat. The prostate gland was palpable rectally

With regard to the hypotonia it may be noted that the tendon reflexes were initially absent in

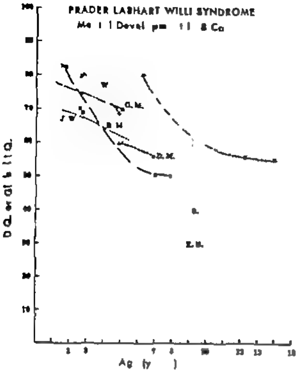


Fig. 15 Prader Labhart Willi syndrome. Mental development in 8 cases.

3 infants, whereas they were present though diminished in 3 others. *After the first year the* tendon reflexes could usually be elicited but they tended to remain sluggish (+1) at least until the second decade. Simultaneously muscle tone improved, but mild hypotonia usually remained, with some laxity of joints and pes planus.

Seven out of 9 children had either a definite squint or at least overaction of an inferior oblique muscle. In addition, there was a wide variety of minor congenital stigmata, particularly poor modelling of pinnae (Fig. 12), short toenails, and arched palate. *Two of our patients had narrow* external ear canals as in Down's syndrome, and bilateral *simian creases, clinodactyly* Brushfield spots on the irides, and mongoloid slanting of the palpebral fissures were also noted in 2 cases each.

Dermatoglyphic pattern

Dermatoglyphic analyses were carried out on all the patients by Dr J R. Miller and are presented in detail in appendix. There were no consistent striking aberrations in the dermal configurations.

The digital patterns were unremarkable with the exception of a relatively rare radial loop on the 3rd digit of the *left hand of Case 4* The average total ridge count of 112.8 was low (Canadian population 133.9 $\pm$1.6) Although this appears to be attributable largely to one patient (Case 2) it is of interest that all but one patient (Case 1) were below the average for their sex, and this point regarding ridge count should be clarified in a larger sample.

The palmar patterns appeared to show normal variations. There were no thenar+Int_1 or Int_2 patterns. Loop distal patterns occured in Int_3 and Int_4 with expected frequency. With the exception of one patient (Case 5) who had a A /W^x/A pattern, the hypothenar patterns were unremarkable. *Only one patient (Case 2) had a significant* displacement of the axial triradius (*atd* angle 59 ht 33.3%)

On the hallucal area the patterns were distal loops or whorls. There were no obvious aberrations in plantar patterns.

Development

The growth charts of Cases 1 to 5 demonstrate that the weight tended to be *below* the 16th percentile for at least the first year when the infant often presented feeding problems during the amyotonic phase. In the second or third year the weight rose and abnormal fat deposition on trunk and buttocks was often evident. If we exclude *Case 9 whose food intake may have been severely* restricted we see from Table 1 that the weight rose above the normal range (i.e. above +2 SD for the height-age) at ages varying from 2 to 6 years, with a mean of 3 years $1^1/_2$ months. In contrast, the stature sometimes tended to drop more below the mean *after* the first year (Cases 1 2 5), and growth did not accelerate notably with weight gain.

Table 1 also shows the delay in the passage of developmental milestones. The patients remained sitting freely *at 10 months to $1^1/_2$ years, with a* mean of 13 months, and they learned to walk *freely at 18 to 39 months*, with a mean of 25 months. They were reported to have said the first word with meaning at 10 to 24 months, with a mean of 16 months. Despite the delay in the acquisition of locomotor and language skills these children were usually alert and responsive particularly in their second and third years, and adaptive and *personal-social abilities were relatively* good. As in Down's syndrome the early developmental and even intellectual assessments often gave more hopeful results than later psychometric

tests. Fig. .5 demonstrates this relative downward trend in the D.Q. and I.Q. scores of 8 patients during the pre-school years. Thus the I.Q. level depends upon the age. In our 5 patients above the age of 6 years the latest global I.Q. assessment ranged from about 30 to 56 (Table 1).

INVESTIGATIONS

Radiological studies

X-ray examination of an arm was performed in all 9 patients (see Table 3). In 6 the bones and muscle bulk were both considered normal, but in 3 the long bones appeared slender and poorly mineralized, and in 2 of these the muscle masses were considered abnormally small. After infancy extensive soft fatty shadows were often evident. The *bone age* at the hand and wrist (22) was significantly retarded in all the 6 boys who were x rayed before the age of 4 years, but not in the one girl (Case 4). In two boys (Cases 3 and 5) the delay in the bone age was no longer significant (i.e. less than −2 SC) at 4 years 8 months and 5 years 8 months, respectively whereas in 2 others it was still significant at 8 and $9^1/_2$ years, respectively though to a lessened extent. In the adult male (Case 6) the elbow and knee showed mature bone development at 20 years. The older of the two girls also had a normal bone age at the wrist, hand, elbow and knee at 13 $/_2$ years.

Skull films were obtained in 6 of these children and were generally unremarkable apart from minor abnormalities of the vault in Cases 1 and 2. In the former at years 4 months, the anterior fontanelle was still open and the posterior fossa somewhat wide. In the latter at 1 year 9 months, the anterior fossa appeared somewhat narrow with unusually steep slope of its floor.

A pneumoencephalogram was only performed in one of our patients (Case 8) and proved normal apart from moderate dilatation of the 3rd and lateral ventricles. It was not considered justifiable to carry out this investigation in the other patients.

Electroencephalograms

These were recorded in 5 of our patients on one or more occasions. Each had at least one normal record, but Case 9 (who may have some superimposed brain damage from perinatal anoxia) had bisynchronous spike discharges at $4^1/_2$ years, mainly in the occipital leads, and Case 8 had low voltage irregular fast activity in all head regions as well as some alpha rhythm at $13^1/$ years.

Electromyograms, nerve conduction studies and muscle biopsies

The electromyogram in 4 and motor nerve conduction studies in 6 of our patients gave normal results for the age. Muscle biopsies were normal in 2 children, and in the third (Case 1) showed only somewhat small muscle fibers. In one of the children with a normal biopsy (Case 5) the motor end plates in the *deltoid* muscle were well impregnated with intravital methylene blue and were also shown to be normal. The lateral rectus muscle of the eye contained some fibrous tissue in Case 3.

Blood counts. Serology

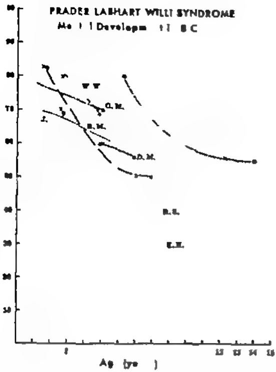
Blood counts were normal in all patients except Case 9 who had a mild anemia, presumably due to iron deficiency. The VDRL serum precipitation or Kahn tests were uniformly negative.

Biochemical studies

Serum electrolyte and blood urea nitrogen levels and routine urinalyses were within normal limits in these patients. The serum cholesterol concentration was examined in 5 cases, and as shown in Table 3 the results were also essentially normal. The urinary amino-acids were checked by paper chromatography in 7 patients and were normal in pattern and quantity. The serum protein-bound iodine (PBI) concentration was slightly low (3.4 and 3.8 μg, respectively) in 2 children (Cases 1 and 4) during the second year but there was no clinical evidence of hypothyroidism. In 6 other patients the level of serum PBI was normal.

The urinary excretion of 17 ketosteroids was examined in 6 cases, and the results were within normal limits, though the values of 2.0 mg per 24 hours at 3 years 8 months and 3.32 mg per 24 hours at 4 $/_2$ years in Cases 1 and 3 respectively are both somewhat high. The urinary excretion of 17-ketogenic steroids was examined in 4 children and was unusually high at 9.2 and 6.81 mg per 4 hours, respectively in the same two boys (see 41).

The effect of metyrapone (40 and 50 mg per kg body weight, respectively in 6 divided doses over 24 hours) on the urinary excretion of



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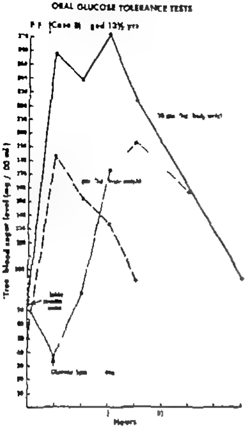

Fig 26 Case 8 P F aged 13 / years. Oral glucose tolerance test.

17 ketogenic steroids was checked in 2 boys, and both exhibited a normal rise to more than twice the original amount (Table 3)

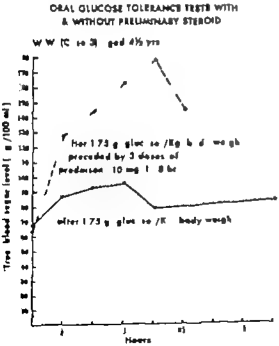

Fig 27 Case 3 W W aged 4 / years. Oral glucose tolerance tests with and without preliminary steroid.

The fasting blood sugar levels of our patients were normal except in R. S. (Case 6) who had levels of 94 110 and 108 mg/100 ml at 20 years. Oral *glucose tolerance tests* were performed in 8 cases, using 1 75 g of glucose per kg body weight up to a maximum of 100 g, and examining skinprick blood by a modified Somogyi Nelson technique *Five out of 8 patients had at least one* high curve, rising above 160 mg/100 ml at 1 hour *or* above 120 mg/100 ml at 2 hours. However since obese children in general often have some impairment of glucose tolerance (67) and the test is influenced by many factors (e g. rate of gastric emptying, previous intake of carbohydrates presence of even mild infections) we thought it best to apply the criteria of Fajans and Conn (*17*) i.e. we considered a curve as diabetic only if the blood sugar level was at or above 160 mg/100 ml after 1 hour 140 *mg* at $1^1/_2$ hours *and* 120 mg after 2 hours By this standard only one patient the girl of $13^1/_2$ years (Case 8), had an abnormal curve (Fig. 26) and this was confirmed in the insulin glucose tolerance test using only 1 g of glucose per kg body weight, so that she is evidently a subclinical diabetic. After priming with cortisone (17) hydrocortisone or prednisone, the glucose tolerance test was repeated in 7 patients. In 3 of these the blood sugar curve rose notably higher than without steroid stress, and in 1 of them (Case 3) it demonstrated a prediabetic state, with a 2 hour blood sugar level of 179 mg/100 ml (Fig. 27) In the two other boys (Cases 7 and 9) the test failed to attain the critical blood glucose level of 140 mg/100 ml at 2 hours.

Insulin sensitivity tests were performed in 2 patients (Cases 6 and 9), 0 1 unit being given i.v per kg *body weight*, and the resulting fall and subsequent rise in the blood sugar level were normal in both.

The fasting *plasma insulin level* was examined in 7 of our cases by Dr J M Martin, of the Hospital for Sick Children in Toronto using the double antibody technique (46). All the values were in the normal range *of 0–20 μU/ml* The plasma insulin values were then determined serially *after* an oral glucose load of 1 g per kg body weight in 5 patients, including the two diabetes suspects (Cases 8 and 3) (Table 4) The $14^1/_2$-year-old girl (Case 8) appeared to have decidedly raised values at 1 to 2 hours, as compared to normal *controls. Three other cases (1*

Table 4 *Plasma insulin levels and oral glucose load tests*

Case No.	Initials	Age (yrs)	Weight (SD above mean for length-age)	Plasma insulin level (μU/ml) after 1 g glucose per kg body weight: Fasting	½ hr p.c.	1 hr p.c.	1½ hrs p.c.	2 hrs p.c.	OTT (1.75 g per kg body weight)	Cortisone (or prednisone) GTT
1	B. M.	8	8	2.5	32.5	30	25	12.5	High normal	Normal
3	W. W.	6	7	10	—	10	25 H	5	Normal	*Abnormal*
4	D. M.	7	+5	0	10	25	15	10	1. Normal 2. Abnormal	Normal
8	P. F.	14½	+3	0	30	45	37	40	*Diabetic*	—
9	E. H.	9½	+6	17.5	2.5	2.5	12.5	0	High normal	High normal
Group average		9		6	20.7	22.5	22.9	13.5		
6 normal controls 7 mos to 10 yrs				10±1.1	16±6	15±0.1	—	14±3.5		

OTT glucose tolerance test. H specimen haemolysed

3 and 4) also had somewhat high levels but these were not so impressive.

Dr J. M. Martin also examined the plasma of 6 of our patients for the presence of the *synalbumin insulin antagonist* described by Vallance-Owen (66,63). The method has been reported previously (15) and reduction of standard insulin activity by more than 50% is usually considered indicative of antagonistic effect, while −40 to −50% is borderline. Only 1 of the 6 children with PLW syndrome (Case 5) showed a significant amount of insulin antagonism (Table 5). We then examined the rest of his family for synalbumin antagonist (Table 6) and found it definitely present in his brother S. and possibly in C. The values of −35.5% in the brother K. and the mother are not strictly significant, but as the trait is evidently dominant (64, 15) one might suspect its presence at least in the mother. On the other hand, there is no history of diabetes in the family at all.

Growth hormone

The plasma levels of growth hormone in 5 patients were determined by Dr J. M. Martin according to the double antibody method described by Morgan (45). The results are listed in Table 7 and are within the normal range.

Gonadotrophin

The urinary FSH excretion was only measured in two cases. In the adolescent patient (Case 6) it was low normal (6–16 mouse uterine units per 24 hours), and in the infant aged 1 year it was already 8 mouse units per 24 hours.

Spinal fluid

The spinal fluid was examined in 2 cases (Case 1 and 3) and proved entirely normal in pressure and composition (cells, protein and sugar content).

Table 5 *Insulin and synalbumin antagonism*

Case No.	Initials	Fasting blood sugar (mg %)	Plasma insulin (μU/ml)	Synalbumin antagonist (%)
1	B. M.	68	10	+41
3	W. W.	81	1	+ 6
4	D. M.	57	2.5	− 8
5	J. W.	67	1	−48
		55	2.5	−86.7
7	P. D.	68	0	+24
8	P. F.	57	9	− 4
9	R. H.	52	17.5	—
	Normal range	50–100	0–20	Less than ±45

Table 6. *Family study of patient with Prader–Labhart–Willi syndrome for synalbumin-insulin antagonism*

Initials	Age (yrs)	Fasting blood sugar (mg %)	Fasting plasma insulin (μU/ml)	Synalbumin antagonist (%)
J. W.	4	55	2.5	−86.7
K. W.	16	67	11.5	−35.5
C. W.	14	64	12.5	−43.6
M. W.	12	58	12.5	−14.2
S. W.	11	67	3.1	−107
Mr W.	41	57	1.5	+40
Mrs. W.	41	59	0	−35.5

Table 7 *Human growth hormone (HGH) levels during glucose tolerance test*

Case No	Initials	Age (yrs)	Plasma HGH level (mμg/ml) after 1 g glucose per kg body weight				
			Fasting	30 min	60 min	90 min	120 min
1	B. M	8	15	14	14	9.5	10
3	W W	6	19	—	15	15	12
5	J W	4	14				
8	P F	14½	19	—	16	12	14 5
9	E. H	9½	17	—	15	13	14

Buccal smear

In 5 boys the buccal smear was chromatin-negative One girl (Case 8) had chromatin-positive cells.

Chromosomes

These were examined in 6 boys and in both girls. Case 1 has an XYY karyotype, and it is noteworthy that this does not appear to have caused any special features in his phenotype which would differentiate him from other cases of the PLW syndrome Two boys (Cases 3 and 9) have a "long Y" of about the same length as chromosomes in the group 16–18 and the father of Case 3 was shown to have a similar Y The father of Case 9 was not examined. Case 3 also exhibited a prominent secondary constriction on the long arm of one of the chromosomes in group 6–12+X in 19 out of 82 cells. The remaining 5 patients had a normal karyotype appropriate to their sex.

Blood groups

The blood of eight of these patients and some members of their families was typed by the Rh Laboratory Winnipeg. The results are shown in the Appendix. So far they have not helped our understanding of the inheritance of the disease but they are recorded here so that they can be added to the studies of other cases in future and thereby facilitate the analysis of larger samples.

DISCUSSION

It will be apparent from these case reports that there is indeed a grouping of *clinical features* amounting to a distinct syndrome as described by Prader and his colleagues. A particular notable feature is the initial hypotonia and weakness, which may have been evident to the mother in poor fetal movements even before birth and which is associated with feeding difficulties during the first year Accordingly the weight gain is usually *below* average in the first year and does not become excessive until the second year This gives the weight curve a characteristic "biphasic" appearance well shown in Figs. 3 6, 13 and 18 Prader and Willi (49) mentioned that the typical obesity develops gradually at about 2 years Evans (16) noted that the weight did not rise above the normal range until a mean age of $2^1/_2$ years, and in our experience the weight only exceeded 2 SD above the mean for the height-age at an average of 3 years $1^1/_2$ months. In contrast to the height of obese children in general, the stature tended to remain below the average for the age, though only 3 of the 9 patients were significantly small Along with the somewhat subnormal growth there was frequently delay in dentition, in closure of the anterior fontanelle and in epiphyseal maturation. Behavioral development was also delayed this delay was particularly marked in the locomotor sphere initially as one might expect with the associated weakness and hypotonia. In general, it seems a valid approximation to say that these children "sit at 1 and walk at 2 years" (49) (see Table 1) However apart from locomotion, the delay also involved language development, and after th first 2–3 years the general mental retardation became increasingly evident (Fig. 25) On physical examination the children showed not only acromicria but also a somewhat characteristic facies with pleasant features, and a variety of minor congenital stigmata (Table 2). Among these we have emphasized the frequent enamel defect and dental caries, and the squints (13 29). The boys also exhibited hypogenitalism which pointed to the

diagnosis in all the 7 males in our series the testes were impalpable and the scrotum was small. The occurrence of diabetes mellitus is inconstant and is usually delayed until the teen years, but may sometimes be predicted by a gradual reduction of glucose tolerance, especially on priming with steroids.

The radiological "*bone age*" at the hand and wrist (22) was significantly low in all the 6 boys who were examined before the age of 4 years but not in the one girl (Case 4). After that age epiphyseal maturation may "catch up" although the delay was still significant (over −2 SD) at nearly 8 and 9 / years in Cases 1 and 9 respectively. This delay in bone age was also noted by Prader *et al.* (48), Evans (16) and Dubowitz (10). Retarded bone age was not found in the 4 cases recorded by Hooft and his colleagues (29), and it may be relevant that 3 of these were girls.

Skull x-rays have generally shown little abnormality apart from minor deformities of the vault. *Pneumoencephalograms* have been performed in several published cases and have usually either been normal (49, 4, 16, 29), or shown moderate ventricular dilatation as in our Case 9 (18, 29). Slight cortical atrophy was suspected in one patient (16). The spinal fluid has generally been normal in pressure and in cell, protein and sugar content, and presumably any ventricular dilatation is secondary to cerebral maldevelopment or atrophy.

The *electroencephalogram* is commonly within normal limits for the age (49, 4, 16, 29), and our 5 patients, in whom the EEG was checked, had at least one normal record each. However immature patterns for the age may be encountered (18) as in other retarded children, and some dysrhythmias have been observed as in our Cases 8 and 9. Thus symmetrical slow waves at 3 cycles per second were noted in one of Royer's (55) patients and bilateral theta rhythms were dominant in the case described by Sánchez Villares *et al.* (56), while one of Hooft's (29) patients had sharp and slow waves posteriorly. One may speculate whether such dysrhythmias could be secondary to anoxic cerebral insults, particularly in the perinatal period. Zellweger and his co-authors (7*) commented on the frequent absence of sleep spindles. Gross epileptiform patterns and clinical seizures are evidently uncommon (cf. Evans (16) Case 7).

The *electromyogram* was normal in 4 of our patients. It was also normal in 3 of Evans (16), 3 of Hooft's (29) and 5 of Laurance's (39) cases. In Hooft's remaining patient (No. 3) and in that of Sánchez Villares (56) evidence of denervation was said to have been found. *Motor nerve conduction studies* were carried out in 6 of our children, particularly in median nerves, and the results were always within normal limits (cf. 20, 11). Nerve conduction was also normal in a few other recorded cases (18, 29). *Muscle biopsies* in 3 of our patients were essentially normal, although Case 1 appeared to have somewhat small muscle fibers, as has been reported in some cases of benign congenital hypotonia (21). In previously recorded patients the muscle biopsy has usually proved normal. Only in one case it is said to have shown neurogenic atrophy (56). In one other intravital staining demonstrated some finely beaded fibers in the smaller nerve bundles (39). Our own findings suggest that there is usually no evidence of any lower motor neurone or muscle disease in these children despite the marked hypotonia and depressed tendon reflexes in infancy.

Endocrine disturbances

In view of the small stature and retarded bone age *thyroid function* has often been investigated. In general, the serum protein-bound iodine (PBI) level has been found to be normal (16, 29). In a 17 year-old patient with borderline low serum PBI and low radioactive iodine uptake, thyroid function responded well to the administration of thyrotropic hormone; this suggested pituitary dysfunction rather than primary hypothyroidism. Similarly although two of our patients exhibited slightly low levels of serum PBI (3.4 and 3.8 μg/100 ml) in their second year they presented no clinical signs of hypothyroidism and subsequently maintained a normal serum PBI concentration after a course of thyroid therapy. Six other patients had PBI levels within the normal range.

In regard to *adrenocortical function* it must be kept in mind that obese children generally tend to exhibit some overactivity of the adrenal cortex (see 69). Accordingly Cohen (6) found the urinary excretion of 17 ketogenic steroids to be

* Personal communication by J. Landwirth, A. H. Schwartz and I. A. Grant (74).

Table 7 *Human growth hormone (HGH) levels during glucose tolerance test*

Case No.	Initials	Age (yrs)	Plasma HGH level (mμg/ml) after 1 g glucose per kg body weight				
			Fasting	30 min	60 min	90 min	120 min
1	B. M	8	15	14	14	9.5	10
3	W W	6	19	—	13	15	12
5	J W	4	14				
8	P F	14½	19	—	18	12	14.5
9	E. H.	9½	17	—	15	13	14

Buccal smear

In 5 boys the buccal smear was chromatin-negative. One girl (Case 8) had chromatin positive cells.

Chromosomes

These were examined in 6 boys and in both girls Case 1 has an XYY karyotype, and it is noteworthy that this does not appear to have caused any special features in his phenotype which would differentiate him from other cases of the PLW syndrome. Two boys (Cases 3 and 9) have a "long Y" of about the same length as chromosomes in the group 16–18 and the father of Case 3 was shown to have a similar Y The father of Case 9 was not examined. Case 3 also exhibited a prominent secondary constriction on the long arm of one of the chromosomes in group 6–12+X in 19 out of 82 cells. The remaining 5 patients had a normal karyotype appropriate to their sex

Blood groups

The blood of eight of these patients and some members of their families was typed by the Rh Laboratory Winnipeg The results are shown in the Appendix. So far they have not helped our understanding of the inheritance of the disease, but they are recorded here so that they can be added to the studies of other cases in future and thereby facilitate the analysis of larger samples.

DISCUSSION

It will be apparent from these case reports that there is indeed a grouping of *clinical features* amounting to a distinct syndrome as described by Prader and his colleagues. A particular notable feature is the initial hypotonia and weakness, which may have been evident to the mother in poor fetal movements even before birth and which is associated with feeding difficulties during the first year Accordingly the weight gain is usually *below* average in the first year and does not become excessive until the second year This gives the weight curve a characteristic biphasic appearance well shown in Figs. 3 6 13 and 18. Prader and Willi (49) mentioned that the typical obesity develops gradually at about 2 years Evans (16) noted that the weight did not rise above the normal range until a mean age of $2^1/_2$ years, and in our experience the weight only exceeded 2 SD above the mean for the height-age at an average of 3 years $1^1/_2$ months. In contrast to the height of obese children in general the stature tended to remain below the average for the age, though only 3 of the 9 patients were significantly small Along with the somewhat subnormal growth there was frequently delay in dentition, in closure of the anterior fontanelle and in epiphyseal maturation Behavioral development was also delayed this delay was particularly marked in the locomotor sphere initially as one might expect with the associated weakness and hypotonia. In general it seems a valid approximation to say that these children "sit at 1 and walk at 2 years" (49) (see Table 1) However apart from locomotion, the delay also involved language development, and after the first 2–3 years the general mental retardation became increasingly evident (Fig. 25) On physical examination the children showed not only acromicria but also a somewhat characteristic facies with pleasant features, and a variety of minor congenital stigmata (Table 2) Among these we have emphasized the frequent enamel defect and dental caries, and the squints (13 29). The boys also exhibited hypogenitalism which pointed to the

early stages of diabetes mellitus. Karam and his colleagues (32) claim that excessive serum insulin responses to a glucose load are more closely correlated with obesity *per se* than with the diabetic state, and Grodsky *et al.* (23) consider that such responses may be of limited value as a sign of prediabetes. On the other hand, Yalow *et al.* (70) find that plasma insulin responses to glucose are somewhat higher than normal in obesity without diabetes but much greater than normal in mild or moderate untreated diabetes of the maturity onset type. We thought it worthwhile to investigate this in our patients, but the results are equivocal. After an oral glucose load in 5 cases the plasma insulin level appeared to rise abnormally in the subclinically diabetic girl, but only to borderline high values in 3 others as compared to 6 controls (Table 4).

A search for excessive synalbumin antagonism to insulin was also considered indicated, since it has been claimed that this can be regarded as a biochemical marker of "essential diabetics" (64). However although Vallance-Owen's (63) preliminary observations indicate that 20 to 25% of the population may be so constituted, Dr. J. M. Martin found significant synalbumin antagonism in only one of 6 patients in our series (Table 5). At least one of this boy's brothers also exhibited such insulin antagonism (Table 6) but it is interesting that there is no history of diabetes in his family.

In future investigations of the pre-diabetic state it may be rewarding to measure the degradation rate of insulin (60) and the blood levels of non-esterified fatty acid (NEFA). According to the hypothesis proposed by Randle and his colleagues (51), the fasting plasma concentration of NEFA may be increased in diabetes mellitus of the maturity-onset type despite elevated concentrations of glucose and high levels of insulin. After an oral glucose load the plasma concentration of NEFA may then only fall slowly and may impair glucose tolerance and insulin sensitivity. The serum levels of lipids and lipoproteins may also be relevant and have been measured in some cases of the PLW syndrome (4, 29, 39). On the other hand, some recent studies suggest that tests directly concerned with glucose metabolism, and particularly the cortisone-glucose tolerance test, are still most likely to prove useful in demonstrating the pre-diabetic state (53).

It is tempting to suspect a *hypothalamic defect* in this syndrome, since such a defect might explain not only the small stature, hypogenitalism and delayed puberty (in males), but also the obesity and even the tendency to diabetes mellitus. Bilateral lesions in or along the lateral border of the ventromedial nuclei of the hypothalamus in rats cause hyperphagia and obesity (27), and electrical stimulation of the lateral part of the hypothalamus in cats and goats also increases food intake (37). Hence a ventromedial "satiety center" and a lateral "feeding center" have been postulated. Ablation of the ventromedial nuclei also reduces spontaneous activity and thereby contributes to weight gain. In animals selective permeability or transport of glucose and tracer substances into this "satiety center" has been demonstrated (37, 43). Thus a defect of satiety could be due to a structural or functional abnormality in this region. To explain the aphagia and anorexia during early infancy in the PLW syndrome Evans (16) has further suggested that the lateral centers in the hypothalamus may mature late in these patients.

It has also been proposed that the "satiety center" acts primarily by exerting "lipostatic" control, i.e. by stabilizing the body's fat stores. The nature of the messenger substance which normally influences the activity of the area is uncertain, but it might be insulin (34). Hales and Kennedy (24) showed that hyperphagic rats which had lesions in the ventromedial nuclei and unlimited access to food for 3 months, had significantly higher plasma concentration of NEFA and insulin after feeding than untreated control animals, and the plasma levels of both substances remained increased after starvation for 24 hours. These abnormalities resemble those in human obesity and in diabetes mellitus of the maturity-onset type. Since a high plasma level of NEFA causes insulin resistance, the consequent increase in the secretion of insulin could eventually lead to functional insufficiency of pancreatic β-cells and thus to the diabetic state. In any case, it has been shown in monkeys and rodents that bilateral electrolytic lesions of the ventromedial nuclei of the hypothalamus cause not only hyperphagia and obesity, but will also lead to diabetes mellitus in a proportion of the animals (25, 26).

Gonadal atrophy and interruption of growth have also been produced by hypothalamic lesions

elevated in such children, while the excretion of 17 ketosteroids was usually at the upper limit of the normal range or only slightly raised. This appeared to be an effect of overnutrition, since weight reduction was invariably associated with a fall in the excretion of both types of steroid. Our own results are in accord with these findings. The urinary excretion of 17 ketogenic steroids appeared unusually high and that of 17-ketosteroids also somewhat high in two boys (Case 1 and 3) who were obese and gaining weight rapidly at 3 years 8 months and 4½ years, respectively (see 41) The excretion of 17 ketogenic steroids was normal in Case 1 at an earlier age and also in two other patients. The excretion of 17 ketosteroids was also normal earlier in Case 1 and at various ages in 4 other patients (see Table 3) In Laurance s (39) cases adrenocortical function also appeared normal when assessed by serum electrolyte levels, water load tests, steroid excretion and response to ACTH.

In this connection, two points should be noted. First, Prader and his colleagues (47) found the excretion of 17 ketosteroids in the older patients strikingly reduced, and in the 43-year-old male described by Juul and Dupont (31) it was at the lower limit of the normal range (9 8 mg per 24 hours). The latter patient also had a low level of plasma testosterone and of urinary androsterone. The reduced production of 17 ketosteroids is probably due to *hypofunction of the testes* rather than the adrenals, for it is also known that the urinary excretion of gonadotrophin and FSH in the syndrome may be raised after puberty (49 31) The question then arises whether the cryptorchidism may at times be associated with marked dysgenesis or atrophy of the testes. Testicular biopsies have only been described in 4 patients and have not shown any gross dysgenesis of tubules but the appearances usually encountered in infantile or abdominal testes and variable reduction in the number of Leydig cells (72, 4 39) Testicular function may vary in different cases. In one of Evans (16) patients, aged 16 years, and in our case 6, at 20 years, the urinary excretion of 17 ketosteroids and of FSH were within normal limits. In general, the presence of the prostate gland and of puberty changes (albeit often delayed and incomplete) indicate at least partial testicular functioning, and thus is also suggested by the increased excretion of androsterone after injection of human chorionic gonadotrophin (44)

Secondly the *pituitary-adrenal relationships* have been investigated with divergent results. Bühler *et al* (4) Forssman and Hagberg (18) and Sugarman and Boder (61) noted that the levels of urinary 17-hydroxycorticosteroids in their respective patients did not rise satisfactorily after administration of either corticotrophin or metyrapone. Other authors have found a normal response to corticotrophin (16 29 39) and in our Cases 3 and 9 as well as in 6 other patients in the literature the metyrapone test gave normal results (36 44 29 39). In connection with the latter test, Laurian and his colleagues (40) have recently pointed out that obese children frequently show a poor response to metyrapone, and particularly boys with "gynoid type of obesity"

In future, assays of corticotrophin and of thyroid-stimulating hormone will be of interest in the assessment of *pituitary function* in the PLW syndrome. The levels of growth hormone were normal in 5 of our patients (Table 7) and in one previous case (4) The urinary excretion of gonadotrophin before puberty was low (54 28) or normal (36 39) and subsequently as mentioned, it tended to be normal or raised. To date the clinical and laboratory findings are more in keeping with those found in delayed puberty than in pituitary infantilism (see 9)

The high incidence of the maturity-onset type of *diabetes mellitus* in the syndrome is unusual in pediatric experience and makes the children suitable subjects for a study of the pre-diabetic and subclinical diabetic state. Evans (16) noted that out of 7 patients, 4 had impaired glucose tolerance tests and 2 with normal results had deficient glucose tolerance after cortisone. Royer (55) described the evolution of diabetes in one patient. Applying the strict criteria of Fajans and Conn (17) we found that out of 8 patients, 1 was diabetic (Case 8). Another appeared to have prediabetes on the basis of the prednisone-glucose tolerance test. Five of the others had a somewhat high blood sugar curve on at least one occasion or without steroid priming, but failed to reach significantly high levels at the appropriate time It is, of course, quite possible that some of these may still develop more evidence of diabetes later

There is some divergence of opinion concerning the significance of plasma insulin levels in the

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The *relationship to other presumed hypothalamic syndromes* is still unclear Among inborn defects there is particularly the Laurence-Moon-Biedl syndrome, in which obesity hypogenitalism and mental retardation are also associated with other abnormalities. However the mental retardation is usually only *mild* and the *accompanying* defects (particularly polydactyly and retinitis pigmentosa) are different. Weiss (68) described a variant of that syndrome, in which "cerebral adiposity" mental deficiency and "genital dystrophy" were combined with nerve deafness instead of retinitis pigmentosa. Solis-Cohen and Weiss (59) noted the occasional occurrence of diabetes mellitus with Fröhlich's syndrome (adiposogenital dystrophy) Alström and his colleagues (1) described 3 cases of a new syndrome, in which obesity and atypical retinal degeneration were associated with nerve deafness and diabetes mellitus. There was no mental retardation and no gross hypogenitalism, but testicular biopsy in one case showed some tubular sclerosis. Finally Lynch and his co-workers (42) recently reported a large kindred which included two siblings showing *juvenile* diabetes mellitus, hyperlipemia, hypogonadism and dwarfism. In addition, varying combinations of juvenile and late-onset diabetes mellitus with hyperlipemia and short stature were found in many relatives. However mental deficiency obesity and hypotonia were not observed in that pedigree

Incidentally the PLW syndrome forms an interesting contrast to a possible diencephalic syndrome of lipodystrophy and gigantism with associated endocrine manifestations (58) Patients affected by that syndrome are thought to have a congenital lack of subcutaneous fat and have an emaciated appearance. *They also have an increased* rate of growth with an acromegaloid pattern and *large* hands and feet, and they exhibit generalized muscular hypertrophy In females the labia majora and clitoris are moderately hypertrophic. Disturbances of carbohydrate metabolism may also occur in that condition, and although the intelligence is usually normal it may be subnormal and the pneumoencephalogram may indicate some cerebral atrophy

Genetic aspects

The *chromosomes* of our patients are noteworthy (Table 3). Case 1 is the only recorded instance of the Prader–Labhart–Willi syndrome *with an XYY karyotype Prior to mid-1965 only 11 instances of this particular chromosome abnor*mality had been reported, and there did not appear to be any consistent associated clinical picture (2) Indeed, the first recorded patient with *this karyotype had no genital or gross somatic* anomalies, though he was tall and obese. He was discovered on routine testing, as he was the father of a girl with Down's syndrome and of other abnormal offspring (57) Similarly patients with the XXYY chromosome abnormality showed clinical features of Klinefelter's syndrome very much like those with the XXY karyotype, with the possible exception of greater skeletal maturation and a more abnormal dermatoglyphic pattern in XXYY cases (3 62) It was therefore thought that the Y chromosome bore relatively little genetic information, compared with the autosomes and the X chromosomes, other than that concerned with male sex determination. Our Case 1 supported this concept, since his phenotype is closely similar to that of other patients with the PLW syndrome who have normal chromosomes. In 1965–66 it was *reported that 9 instances of XYY* males were found among 315 patients with aggressive and violent propensities in a mental hospital (30 50). Eight of these were high-grade defectives, and 6 were over 6 ft (183 cm) in height there were no other physical abnormalities. In contrast to this high incidence the XYY abnormality was found only once among 2000 male control chromosome counts (35) *Further among 21 chromatin-positive* patients liable to criminal behavior 7 had the XXYY chromosome abnormality whereas usually less than 1 in 10 chromatin-positive cases have this karyotype (5) It therefore seems that an *extra Y chromosome* predisposes to aggressive antisocial behavior and unusually tall stature So

far our Case 1 has not shown either of these characteristics. However his bone age is still significantly retarded at the age of 8 years, so the epiphyses may yet fuse late and allow continued growth.

The presence of a "long Y" chromosome (with the same length as group 16–18) in 2 of the other 5 boys with a known karyotype in our series also deserves comment, for this anomaly is found in fewer than 3% of randomly chosen males (8). Altogether 3 out of 8 patients with known karyotype in our experience thus have at least a minor chromosome anomaly. Further four instances of anomalies affecting group D or E chromosomes, again with little effect on the phenotype, have been recorded with this syndrome, namely a probable translocation of 2 chromosomes (4) and mosaicism for trisomy of a chromosome (54) within the D group and also a 14–18 translocation (71) and an abnormal chromosome No. 16 (10). This total of 7 patients would seem to represent a somewhat high incidence of minor chromosomal anomalies in the approximately 70 cases of the PLW syndrome known to me, although such instances of the condition with associated chromosome abnormalities are perhaps particularly likely to be reported. One may at least speculate whether minor chromosomal aberrations are unduly common in the Prader–Labhart–Willi as in Down syndrome (see 14).

It is evident that the PLW syndrome involves not only the nervous system, even though a hypothalamic defect may go far to explain the endocrine and metabolic derangement. The acromicria, enamel hypoplasia, peculiar facies and many so-called degenerative stigmata (see Table 2) indicate a more widespread disturbance in fetal development. The variable minor aberrations of dermatoglyphic patterns and of chromosomal karyotype in some cases are also in keeping with this concept. No notable diseases have occurred during gestation in the recorded cases, and it seems likely that the cause of the syndrome is genetic. Its various manifestations might then all be due to pleiotropic gene, as suggested by Prader and Willi (49). As to the mode of inheritance it is tempting to suggest that the condition is due to an autosomal recessive trait like the Alström and Laurence–Moon–Biedl syndromes, which show some similar features. It is, however surprising that Gabilan's (19) somewhat atypical patients include the only recorded siblings with the disease and the only recorded child with consanguineous parents. Until more familial aggregation of the syndrome is demonstrated, it is also possible that the condition may be due to a recurrent autosomal dominant mutation (J. R. Miller personal communication).

Treatment

Lastly in the management of this disease we have found that the obesity is as great a problem to the parents as the mental retardation. We have treated the obesity with activation and low-calorie diets, but the appetite seems truly voracious. Phenmetrazine has appeared slightly more effective than the amphetamines in reducing it. In view of the mental defect the question of hormonal or surgical treatment for cryptorchidism rarely arises. In regard to pre-diabetes and subclinical diabetes we have wondered whether tolbutamide might be administered in order to prevent exhaustion of the pancreatic β-cells, but its value in this respect still seems controversial. It was found successful in the treatment of the frank diabetic state by Royer (55) but not by Larbre *et al.* (36).

SUMMARY

In 1956 Prader and his associates described a syndrome of obesity small stature, acromicria and oligophrenia, regularly preceded by an amyotonic state in the newborn period. The males also had a hypoplastic flat scrotum, inguinal or abdominal retention of testes and delayed puberty. A tendency to the development of diabetes mellitus in the teenage years was also noted, and the diabetes was of the type normally encountered with onset at maturity rather than in childhood.

About 70 cases of this syndrome have been published to date. The literature is reviewed, and details concerning 9 patients of our own are given. Seven of these 9 are males: this predominance may be influenced by the fact that the hypogenitalism in boys facilitates the diagnosis. The mean parental ages at the birth of our patients were abnormally high, but this finding has not been encountered by other observers. Clinically in addition to the features described by Prader and his colleagues, these patients presented a normal or somewhat large head circumference, delay

in rats, but the responsive region of the hypothalamus was more diffuse than that concerned in the regulation of appetite and extended through much of the *medial and posterior parts* (33) Another feature in the PLW syndrome which could be explained by a hypothalamic defect is the disturbance in the diurnal variation of plasma 11-hydroxycorticosteroid levels observed in 2 out of 3 patients by Monnens and Kenis (44) No doubt there are more extensive cerebral defects in the syndrome to account for the mental deficiency

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It is evident that the PLW syndrome involves not only the nervous system, even though a hypothalamic defect may go far to explain the endocrine and metabolic derangement. The acromicria, enamel hypoplasia, peculiar facies and many so-called degenerative stigmata (see Table 2) indicate a more widespread disturbance in fetal development. The variable minor aberrations of dermatoglyphic patterns and of chromosomal karyotype in some cases are also in keeping with this concept. No notable diseases have occurred during gestation in the recorded cases, and it seems likely that the *cause of the syndrome* is genetic. Its various manifestations might then all be due to a pleiotropic gene, as suggested by Prader and Willi (49). As to the mode of inheritance it is tempting to suggest that the condition is due to an autosomal recessive trait like the Alström and Laurence–Moon–Biedl syndromes, which show some similar features. It is, however surprising that Gabilan's (19) somewhat atypical patients include the only recorded siblings with the disease and the only recorded child with consanguineous parents. Until more familial aggregation of the syndrome is demonstrated, it is also possible that the condition may be due to a recurrent autosomal dominant mutation (J. R. Miller personal communication).

Treatment

Lastly in the *management* of this disease we have found that the obesity is as great a problem to the parents as the mental retardation. We have treated the obesity with activation and low-calorie diets, but the appetite seems truly voracious. Phenmetrazine has appeared slightly more effective than the amphetamines in reducing it. In view of the mental defect the question of hormonal or surgical treatment for cryptorchidism rarely arises. In regard to pre-diabetes and subclinical diabetes we have wondered whether tolbutamide might be administered in order to prevent exhaustion of the pancreatic β-cells, but its value in this respect still seems controversial. It was found successful in the treatment of the frank diabetic state by Royer (55) but not by Larbre *et al.* (36)

SUMMARY

In 1956 Prader and his associates described a syndrome of obesity small stature, acromicria and oligophrenia, regularly preceded by an amyotonic state in the newborn period. The males also had a hypoplastic flat scrotum, inguinal or abdominal retention of testes and delayed puberty. A tendency to the development of diabetes mellitus in the teenage years was also noted, and the diabetes was of the type normally encountered with onset at maturity rather than in childhood.

About 70 cases of this syndrome have been published to date. The literature is reviewed, and details concerning 9 patients of our own are given. Seven of these 9 are males this predominance may be influenced by the fact that the hypogenitalism in boys facilitates the diagnosis. The mean parental ages at the birth of our patients were abnormally high, but this finding has not been encountered by other observers. Clinically in addition to the features described by Prader and his colleagues, these patients presented a normal or somewhat large head circumference delay

in rats, but the responsive region of the hypothalamus was more diffuse than that concerned in the regulation of appetite and extended through much of the medial and posterior parts (33) Another feature in the PLW syndrome which could be explained by a hypothalamic defect is the disturbance in the diurnal variation of plasma 11 hydroxycorticosteroid levels observed in 2 out of 3 patients by Monnens and Kenis (44) No doubt there are more extensive cerebral defects in the syndrome to account for the mental deficiency

The *relationship to other presumed hypothalamic syndromes* is still unclear Among inborn defects there is particularly the Laurence-Moon Biedl syndrome, in which obesity hypogenitalism and mental retardation are also associated with other abnormalities. However the mental retardation is usually only mild, and the accompanying defects (particularly polydactyly and retinitis pigmentosa) are different. Weiss (68) described a variant of that syndrome, in which "cerebral adiposity" mental deficiency and "genital dystrophy" were combined with nerve deafness instead of retinitis pigmentosa. Solis-Cohen and Weiss (59) noted the occasional occurrence of diabetes mellitus with Fröhlich's syndrome (adiposogenital dystrophy) Alström and his colleagues (1) described 3 cases of a new syndrome, in which obesity and atypical retinal degeneration were associated with nerve deafness and diabetes mellitus. There was no mental retardation and no gross hypogenitalism, but testicular biopsy in one case showed some tubular sclerosis. Finally Lynch and his co-workers (42) recently reported a large kindred which included two siblings showing *juvenile* diabetes mellitus, hyperlipemia, hypogonadism and dwarfism. In addition, varying combinations of juvenile and late-onset diabetes mellitus with hyperlipemia and short stature were found in many relatives. However mental deficiency obesity and hypotonia were not observed in that pedigree

Incidentally the PLW syndrome forms an interesting contrast to a possible diencephalic syndrome of lipodystrophy and gigantism with associated endocrine manifestations (58). Patients affected by that syndrome are thought to have a congenital lack of subcutaneous fat and have an emaciated appearance They also have an increased rate of growth with an acromegaloid pattern and *large* hands and feet, and they exhibit generalized muscular hypertrophy In females the labia majora and clitoris are moderately hypertrophic. Disturbances of carbohydrate metabolism may also occur in that condition, and although the intelligence is usually normal it may be subnormal and the pneumoencephalogram may indicate some cerebral atrophy

Genetic aspects

The *chromosomes* of our patients are noteworthy (Table 3). Case 1 is the only recorded instance of the Prader–Labhart–Willi syndrome with an XYY karyotype. Prior to mid-1965 only 11 instances of this particular chromosome abnormality had been reported, and there did not appear to be any consistent associated clinical picture (2) Indeed, the first recorded patient with this karyotype had no genital or gross somatic anomalies, though he was tall and obese. He was discovered on routine testing, as he was the father of a girl with Down's syndrome and of other abnormal offspring (57) Similarly patients with the XXYY chromosome abnormality showed clinical features of Klinefelter's syndrome very much like those with the XXY karyotype, with the possible exception of greater skeletal maturation and a more abnormal dermatoglyphic pattern in XXYY cases (3 62) It was therefore thought that the Y chromosome bore relatively little genetic information, compared with the autosomes and the X chromosomes, other than that concerned with male sex determination. Our Case 1 supported this concept, since his phenotype is closely similar to that of other patients with the PLW syndrome who have normal chromosomes. In 1965–66 it was reported that 9 instances of XYY males were found among 315 patients with aggressive and violent propensities in a mental hospital (30 50). Eight of these were high-grade defectives, and 6 were over 6 ft (183 cm) in height there were no other physical abnormalities. In contrast to this high incidence, the XYY abnormality was found only once among 2000 male control chromosome counts (35) Further among 21 chromatin-positive patients liable to criminal behavior 7 had the XXYY chromosome abnormality whereas usually less than 1 in 10 chromatin-positive cases have this karyotype (5) It therefore seems that an extra Y chromosome predisposes to aggressive antisocial behavior and unusually *tall stature* So

far our Case 1 has not shown either of these characteristics. However his bone age is still significantly retarded at the age of 8 years, so the epiphyses may yet fuse late and allow continued growth.

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Appendix. *Palmar formulations (Dr J. R. Miller)*

	Main lines				Axial triradius		Patterns				
	D	C	B	A	%	ATD	HT	Th/I1	I2	I3	I4
Case 1											
Left	7	5'	5'	3	17.2	40°	A /A	0	0	0	L
Right	9	7	5'	3HT 13	16.2	45	L /A	0	0	0	L
Case 2											
Left	7	5'	3	4	33.5	59°	A /A	V	0	0	L
Right	9	7	5'	3	13.0	41	A /A	0	0	0	L
Case 3											
Left	9	7	3	3	11.1	51	L /A	0	0	0	L^d
Right	9	7	5'	3HT 11	18.5	51	L /A	0	0	0	L
Case 4											
Left	9	7	5	3HT 11	17.8	51	L /A	0	0	0	L^d
Right	11	9	7	3	13.2	49°	A /A	0	0	L^d	0
Case 5											
Left	11	9	7	3HT 11	12.5	39°	L /A	0	0	L^d	0
Right	11	9	7	4	18.5	48°	A^d/W^d/A	0	0	L	0
Case 6											
Left	9	7	5	3	20.0	41°	A /A	0	0	0	L^d
Right	11	9	7	5'	13.0	37°	A /L /A	0	0	L	0
Case 7											
Left	11	9	7	3	16.0	41	A /A	0	0	L^d	0
Right	11	9	7	5'	13.0	45	A /A	0	0	L^d	0
Case 8											
Left	11	X	7	5'	23.5	45°	A^u/A	0	0	0	0
Right	11	X	7	4	10.6	38°	A^u/A	0	0	0	0
Case 9											
Left	9	7	5'	3	13	40°	A /A	0	0	0	L
Right	9	7	3	4	8.7	40°	A /A	0	0	0	L^d

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Appendix. *Palmar formulations (Dr J. R. Miller)*

	Main lines				Axial triradius		Patterns				
	D	C	B	A	%	ATD	HT	TH+I	I_2	I	I
Case 1											
Left	7	5'	5'	3	17.2	40°	A /A	0	0	0	L^d
Right	9	7	5'	3HT 13	16 2	45°	L /A	0	0	II	L
Case 2											
Left	7	5	5	4	33.3	39°	A /A	V	0	0	L^d
Right	9	7	5	3	15 0	41	A /A	0	0	0	L^d
Case 3											
Left	9	7	3	3	11.1	[illegible]	L /A	[illegible]	0	0	L^d
Right	9	7	5'	3HT 11	18.5	[illegible]	L /A	0	0	0	L
Case 4											
Left	9	7	5'	3HT 11	17.8	51	L /A	[illegible]	0	0	L^d
Right	11	9	7	3	13.3	49°	A /A	[illegible]	0	L^d	[illegible]
Case 5											
Left	11	9	7	3HT-11	12.3	39°	L /A	0	0	L	0
Right	11	9	7	4	18.5	46°	A^d/W^d/A	[illegible]	0	L^d	0
Case 6											
Left	9	7	5	3	20 0	42°	A /A	0	0	0	L
Right	11	9	7	5	13.0	37°	A /L /A	0	0	L	0
Case 7											
Left	11	9	7	5	16.0	43	A /A	0	0	L	0
Right	11	9	7	5	13.0	45°	A /A	0	0	L^d	0
Case 8											
Left	11	X	7	5	23.5	45°	A /A	[illegible]	II	II	0
Right	11	X	7	4	10 8	38°	A /A	0	0	0	0
Case 9											
Left	9	7	5'	3	13	40°	A /A	0	0	0	L
Right	9	7	5	4	8.7	40°	A^d/A	0	0	[illegible]	L

Appendix. *Plantar formulations (Dr J R. Miller)*

	Main lines				Patterns							
	D	C	B	A	HAL	THEN	CAL	HT	HAL	I_2	I	I
Case 1												
Left	9	7	5	1	13	0	0	0	L^d	0	0	L^d
Right	11	9	7	1	13	0	0	0	L^d	0	L^d	0
Case 2												
Left	1	1	1		13	0	0	0	W	0	L^p	0
Right	1	1	1	1	13	0	0	0	W	0	L^p	0
Cases 3												
Left	1	1	1	1	13	0	0	0	L^d	0	0	0
Right	11	11	9	1	13	0	0	0	L^d	0	L^d	0
Case 4												
Left	1	1	1	1	13	0	0	0	W	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0
Case 5												
Left	1	9		1	13/1	0	0	0	W	L^p	L^d	L^d
Right	1	9		9	13	0	0	0	L^d	0	L^d	L^t
Case 6												
Left	1	1	1	1	13	0	0	L^t	L^d	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0
Case 7												
Left	1	9	7	1	13	0	0	0	L^d	0	L^d	0
Right	1	11	9	1	13	0	0	0	L^d	0	L^d	0
Case 8												
Left	1	1	1	1	13	0	0	0	L^d	L^t	0	0
Right	1	1	9	9	13	0	0	0	L^d	L^d	L^d	0
Case 9												
Left	1	1	1	1	13	0	0	0	L^d	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0

Appendix. *Digital patterns and ridge counts (Dr J. R. Miller)*

	Left 5	Left 4	Left 3	Left 2	Left 1	Total	Right 1	Right 2	Right 3	Right 4	Right 5
Case 1	Lu	Lu	Lu	W	W		W	W	Lu	Lu	Lu
	16	18	9	15	17	75/144/69	17	16	9	12	15
Case 2	Lu	Lu	Lu	A	Lu		W	A	Lu	Lu	Lu
	7	9	1	0	3	20/58/38	14	0	3	9	12
Case 3	Lu	Lu	Lu	W	Lu		W	W	Lu	Lu	Lu
	3	5	7	25	25	65/123/58	24	15	3	3	13
Case 4	Lu	Lu	Lr	Lr	W		W	Lr	A	Lu	Lu
	16	14	5	15	18	68/123/55	18	11	0	14	12
Case 5	Lu	Lu	Lu	Lu	W		W	W	Lu	Lu	Lu
	13	15	9	14	14	65/129/64	16	13	12	12	11
Case 6	Lu	Lu	Lu	A	W		W	A	Lu	Lu	Lu
	19	4	2	0	21	46/89/43	21	0	2	6	14
Case 7	Lu	Lu	Lu	Lu	Lu		W	Lu	Lu	Lu	Lu
	17	12	10	12	13	62/127/65	13	16	10	13	13
Case 8	Lu	Lu	Lu	Lu	Lu		Lu	Lu	Lu	W	Lu
	12	13	4	1	10	40/85/45	9	8	4	13	11
Case 9	W	W[d]	Lu	W	W[d]		W		Lu	W	Lu
	18	16	14	14	16	78/137/59	21		16	12	10

Appendix. *Plantar formulations (Dr J R. Miller)*

	Main lines				Patterns							
	D	C	B	A	HAL	THEN	CAL	HT	HAL	I_2	I	I
Case 1												
Left	9	7	5	1	13	0	0	0	L^d	0	0	L^d
Right	11	9	7	1	13	0	0	0	L^d	0	L^d	0
Case 2												
Left	1	1	1		13	0	0	0	W	0	L^p	0
Right	1	1	1	1	13	0	0	0	W	0	L^p	0
Cases 3												
Left	1	1	1	1	13	0	0	0	L^d	0	0	0
Right	11	11	9	1	13	0	0	0	L^d	0	L^d	0
Case 4												
Left	1	1	1	1	13	0	0	0	W	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0
Case 5												
Left	1	9		1	13/1	0	0	0	W	L^p	L^d	L^d
Right	1	9		9	13	0	0	0	L^d	0	L^d	L^d
Case 6												
Left	1	1	1	1	13	0	0	L^t	L^d	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0
Case 7												
Left	1	9	7	1	13	0	0	0	L^d	0	L^d	0
Right	1	11	9	1	13	0	0	0	L^d	0	L^d	0
Case 8												
Left	1	1	1	1	13	0	0	0	L^d	L^t	0	0
Right	1	1	9	9	13	0	0	0	L^d	L^d	L^d	0
Case 9												
Left	1	1	1	1	13	0	0	0	L^d	0	0	0
Right	1	1	1	1	13	0	0	0	L^d	0	0	0

Appendix. *Blood group studies* (*Rh Laboratory Winnipeg*)

Case			ABO	MNSs	P	Rh	Le a	Fy b	Jk a b	Xg a	Bl	Be a	Mi a	V_w	D^w	By a	Di a	LW	Wr a	Re^a	Bu a	Vel	Yt a	Cr a
1	B. M	F	B	MNs	+	R_1r		−+	++			−	−	−	−	−								
		M	O	MNs	+	R_1		++	++	−		−	−	−	−	−								
			[illegible]	Ms	+	R		++	+−	−		−	−	−	−	−								
2	G M		O	MNs	+	R r	−	−+	−+			−	−	−		−	−							
		♀	O	Ms	+	R R	−	++	++			−	−	−		−	−							
3	W W	F	O	MS	+	R_1R_2		++	+−			−	−											
		M	A B	NSs	+	[illegible]		+−	+−			−	−											
			A	MNSs	+	R R_2		+−	+−			−	−											
4	D M	F	O	MS	+	R_2r	−	++	+−	−	−	−			−			+	−	−				
		M	B	Ms	+	R r	−	−+	+−	+	−	−			−			+	−	−				
		♀	B	MSs	+	r	−	−+	+−	+	−				−			+						
		♀	O	MSs	+	R r	+	−+	+−	−	−				−			+						
		♂	O	MSs	+	r	−	++	+−	−	−				−			+						
5	J W	F	O	MNs	+	r	−	−+	+−	−	−	−	−	−		−					−			
		M	O	MNSs	+	R r	−	++	++	+	−	−	−	−		−					−			
		●	O	Ns	+	R r	+	−+	+−		−	−	−	−		−								
7	P D	F	O	MNs	+	R R_2	−	++	++	+	−	−			−			+	−	−				
		M	A	MNs	+	R r	−	++	++	−	−	−			−			+	−	−		+	+	
		♂	O	MNs	+	R_2	−	+−	−+	−	−				−			+					+	
		♀	A_2	Ns	+	R r	+	++	++	+	−				−			+				+		
			O	Ms	+	R R_2	−	+−	+	−	−				−			+				+		
8	P F	F	O	MNs	+	R R_2	−	−+	++	−	−	−			−			+	−	−		+	+	+
		M	A	MNs	+	R r	−	++	++	+	−	−			−			+	−	−			+	
		♂	A	MNs	+	R r	−	++	++	+	−				−			+				+	+	
		♀	O	MNs	+	R	−	−+	++	+	−				−			+				+	+	
		♂	A	MNs	+	R	−	−+	+−	+	−				−			+				+	+	
		♀	O	M	+	R r	−	++	++	+	−				−			+				+	+	
		♂	O	MNs	+	R R_2	−	++	−+	+	−				−			+				+	+	
9	E. H.	F	B	MNs	+	R R_2		−+	++	−	−	−			−			+	−	−	−			
		M	A	MSs	−	R_2r		−+	−+	+	−	−			−			+	−	−	−			
		♀	O	MNSs	−	R_2		−+	++	+	−				−			+						
		♂	O	Ms	+	R_2r		−+	−+	+	−				−			+						
		●	O	MSs	+	R_2r		−+	−+	+	−				−			+						
		♂	B	MNs	−	R_2r		−+	−+	+					−			+						
		♀	A [illegible]	MNs	+	R		−+	−+	+	−				−			+						

F = Father M = Mother or ♀ = Propositus. ♂ or ♀ = Sibling.
All blood grouping recorded as phenotypes. All C^w − K k+ Kp(−b+) *Father and propositus of Family 5 Le(+b* all others Le(a − b +).
Re = Reid, a low frequency a tigen discovered by Dr Raymond Guevin

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 185 1968

SKELETAL MATURATION OF DANISH SCHOOL CHILDREN IN RELATION TO HEIGHT, SEXUAL DEVELOPMENT, AND SOCIAL CONDITIONS

BY ELSE ANDERSEN

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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Translated from the Danish

by

Anna le Cou née Claessen.

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Denne afhandling er af det lægevidenskabelige fakultet
ved Københavns Universitet antaget til offentligt
at forsvares for den medicinske doktorgrad.

København, den 4. marts, 1968

Mogens Faber
h. a. dec.

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Introduction

The present investigation comprised a cross-sectional study of skeletal maturation of the hand and wrist in a series of Danish school children aged 7–18 years. Skeletal maturity was related to the children's age, stage of puberty and to the environment in which they were raised. The results were also compared with similar results from other countries.

The physical development of children of the same chronological age may vary within wide limits. The biological variation for a given chronological age is least for the younger ages, increasing gradually up to a maximum around puberty and then decreasing slightly.

Fig. 1 illustrates Broman, Dahlberg & Lichtenstein's (1942) curves representing the height of Swedish boys ± 1 and 2½ standard deviations, SD. It is apparent from the curve that chronological age is not a good standard of maturity since a boy of, say 14 years may measure between 139 and 180 cm and yet be of normal height.

Height is also no accurate standard of maturity as a boy of 130 cm may be from 9 to 16 years of age and yet fall within the normal range.

Sometimes a child's development is expressed in terms of its *height age* i.e. the average age at which children of the same sex attain a given height. The height age, when compared with the chronological age, indicates whether the child's growth is retarded or advanced in relation to the average.

Figs. 2 and 3 show Tanner's (1963) diagrams presenting the sequence of the various signs of puberty and the age range within which they appear. Two boys of say 14 years may differ widely in maturity. One may be in full puberty with incipient growth of beard, a deep voice, and fully developed in respect to pubic and axillary hair and genitalia, while the other may be slight and boyish with infantile secondary sex characters.

Because of this great difference in the age at which children enter puberty and because puberty entails such extensive changes in body size, physiology and pattern of behaviour, the mere fact that a boy is 14 years of age does not say much concerning his stage of development. All depends upon whether he is pre-adolescent, mid-adolescent or post-adolescent (Tanner 1963).

Therefore, a search has been made for other ways of assessing the stage of development.

Introduction

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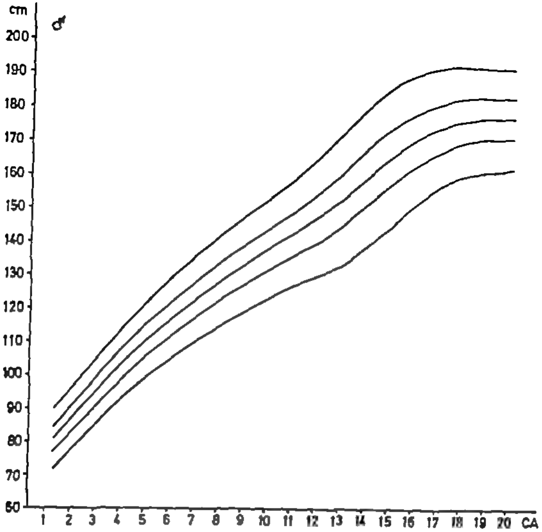


Fig 1

Height of Swedish boys ± 1 and ± 2 /s SD (Broman Dahlberg & Lichtenstein 1942)

Crampton (1908) introduced the concept *physiological age* defined as the number of years which have elapsed since pubescence, i.e. the appearance of pubic hair

In evaluating *biological age* meaning general physical development, criteria such as pubic and axillary hair size of testes, breast development, and menarche have been used During adolescence, i.e. the period of puberal development, these criteria express the stage of development quite well But there was a need for a method by which biological development may be assessed before, during and after puberty

Skeletal maturation has proved to be a graded and fairly accurate standard for assessment of biological age *Skeletal age* expresses the stage of skeletal maturation.

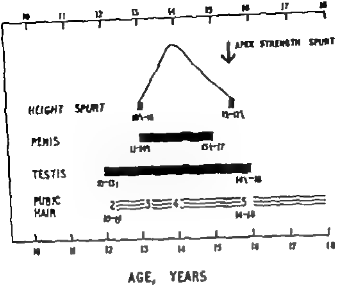
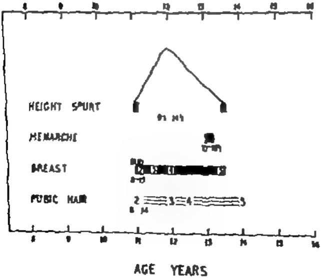


Fig 2

Diagram showing the sequence of the various signs of puberty and the ages within which they appear Boy (Tanner 1963)



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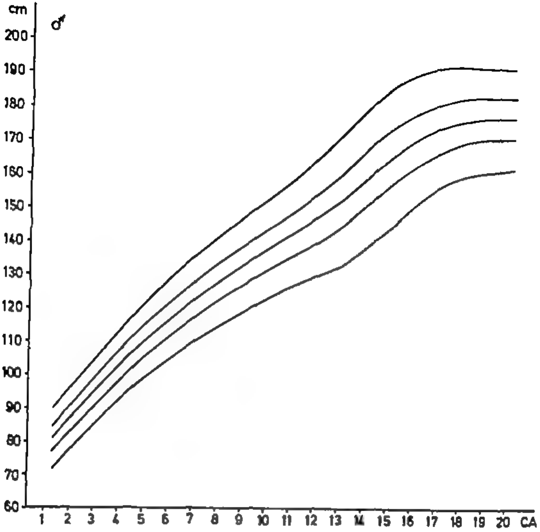

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Chapter I

Skeletal Maturation and Methods of Assessment

In the 19th century bones and skeletal maturation were studied by dissecting cadavers. After the detection of X rays in 1895 it was possible to study skeletal maturation in living persons, so that minute differences could be demonstrated by longitudinal investigations.

Formation and Maturation of Long Bones

In a newborn infant a long bone consists of an osseous shaft, the preliminary diaphysis. The bone ends are made of cartilage resembling the final bone. The ossification centres of the bone ends, i.e. secondary centres or epiphyseal centres, usually do not appear until after birth. An exception is the appearance of the epiphyseal centre in the distal part of the femur Beclard's (1820) ossification centre, shortly before birth, in the 9th foetal month. This applies to children of a birth weight ≥ 3000 g (Christie 1949) Frequently the epiphyseal centre in the proximal end of the tibia too is present before birth. The longitudinal growth of the long bones takes place at the diaphyseal ends where they are in contact with the epiphyseal cartilage. Gradually as the epiphysis ossifies, the epiphyseal cartilage is reduced to a narrow disc between the diaphysis and epiphysis. When epiphyseal closure is completed, longitudinal growth must be considered to have ceased.

Maturation of the Hand Skeleton

A number of studies which have contributed to our present knowledge of postnatal skeletal maturation will be reviewed below As the present study concerns the maturation of the hand skeleton, it is natural to concentrate particularly on investigations dealing with the skeletal maturation in the hand and wrist.

The times and the order of appearance of the ossification centres of the carpal bones and epiphyses in the hand have been studied int. al. by Pryor (1907) Todd (1937) Francis & Werle (1939) Robinow (1942) Pyle & Sontag (1943) Stuart & Stevenson (1954) and Garn & Rohmann (1960 a)

The sequence of epiphyseal fusion in the hand has been studied by Todd, Garn, Rohmann & Apfelbaum (1961) Pyle, Stuart, Cornoni & Reed (1961) and Stuart, Pyle, Cornoni & Reed (1962) All these investigations were longitudinal.

Tables 1 and 2 give, for boys and

Object of the Study

As no studies of the skeletal development of Danish children exist their skeletal maturity can be assessed only by foreign systems. A number of earlier and more recent foreign studies, int. al. in the form of standard tables and atlases, are available for assessing the normal skeletal maturation of children and adolescents. It was the object of the present study to assess the applicability of various foreign systems on a Danish normal series, to investigate the value of skeletal maturity as a parameter of the children's biological age, and lastly to assess whether differences in social circumstances influenced skeletal maturation. As it has been demonstrated that skeletal maturation may take place at different rates in different environments and at different times, it cannot be taken for granted that foreign norms are applicable unmodified in Denmark.

It is of practical importance to be able to determine the skeletal age and thus the stage of general physical development in conditions and diseases which entail disturbances of growth and maturation, partly because skeletal age is an important diagnostic aid and partly because it is a criterion which can tell us whether an instituted treatment is working.

It was decided to include children and adolescents in the age range 7–18 years, i.e. the ages before, during and after puberty because it is particularly within these age groups that children present problems concerning growth and maturation and because in the younger age groups height is quite a good standard of development.

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Table 1

Ages of onset and completion, and the span of development of 29 ossification centres of *the hand and wrist (Stuart, Pyle Cornoni & Reed)*

Boys.

Bone	Mean onset, order	Number	Onset		Completion		Span	
			M	SD	M	SD	M	SD
Capitate	1	56	2.9	1.7	183	12	180	1
Hamate	2	56	4.2	2.7	183	12	179	11
Radius	3	25	12.3	5.3	208	8	196	11
Finger 3 prox. phal. epiph.	4	57	16.4	4.6	191	12	175	12
Finger 2 prox. phal. epiph.	5	56	17.2	4.8	191	13	174	13
Finger 4 prox. phal. epiph	*6*	*56*	*18.1*	*5.0*	*191*	*13*	*173*	*13*
Metacarpal 2 epiph.	7	56	19.3	5.5	194	13	175	13
Finger 1 distal phal. epiph.	8	58	20.6	6.8	184	13	163	14
Metacarpal 3 epiph.	9	56	21.8	6.9	195	13	173	14
Finger 5 prox. phal. epiph.	*10*	*56*	*23.8*	*6.7*	*191*	*13*	*167*	*14*
Metacarpal 4 epiph.	11	56	24.8	7.3	194	13	170	14
Finger 3 middle phal. epiph.	12	56	25.1	6.2	192	13	167	14
Finger 4 middle phal. epiph.	13	56	26.0	6.2	192	13	166	14
Finger [illegible] middle phal. epiph.	*14*	*56*	*27.1*	*7.1*	*191*	*12*	*164*	*14*
Metacarpal 5 epiph.	15	56	27.1	8.6	196	14	168	15
Triquetral	16	57	29.5	16.2	183	12	153	[illegible]
Finger 3 distal phal. epiph.	17	57	30.7	7.1	186	13	156	13
Finger 4 distal phal. epiph.	*18*	*57*	*31.2*	*7.4*	*186*	*13*	*155*	*14*
Metacarpal 1 epiph.	19	56	34.8	11.1	187	14	152	16
Finger 1 prox. phal. epiph.	20	56	36.3	9.1	191	13	155	15
Finger [illegible] distal phal. epiph.	*21*	*57*	*41.[illegible]*	*9.0*	*185*	*13*	*144*	*14*
Finger 5 distal phal. epiph.	*22*	*57*	*41.9*	*10.1*	*186*	*13*	*144*	*13*
Lunate	23	58	43.5	14.7	183	11	140	16
Finger 5 middle phal. epiph.	24	56	44.4	11.9	190	13	146	15
Navicular	25	58	69.6	15.4	183	11	113	17
Lesser multangular	26	58	72.0	16.1	183	11	111	15
Greater multangular	27	58	72.7	18.4	183	11	110	19
Ulna	28	26	80.3	13.4	205	10	124	16
Adductor sesamoid (thumb)	29	50	150.8	13.7	192	14	41	14

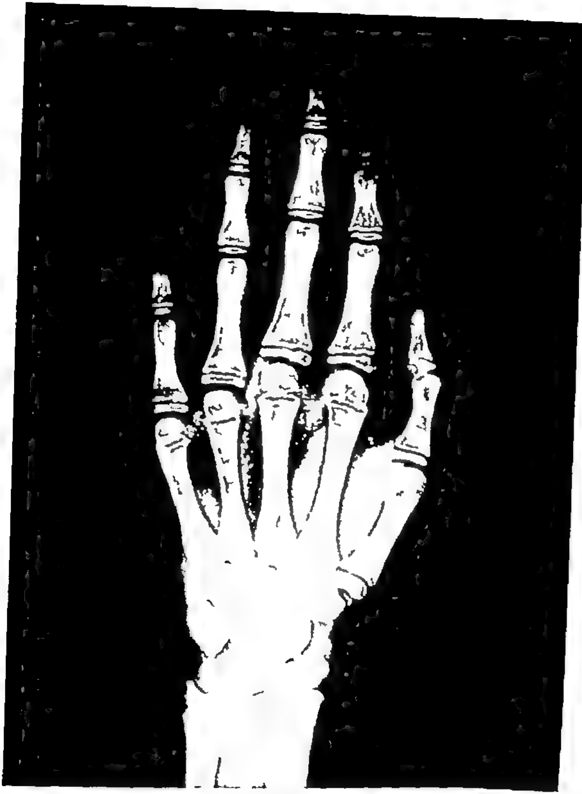
Means (M) and standard deviations (SD) are expressed in months.

girls respectively the onsets and sequence of the ossification centres, the times and sequence of epiphyseal fusion with the shaft and the spans from the onset of ossification until the process has been completed. The figures are derived from the study of Stuart Pyle, Cornoni & Reed which is the most comprehensive one.

At birth the hand and wrist show ossification centres only in the diaphyses of the metacarpal and phalangeal bones. In the course of the first 6 or 7 years of life 28 new ossification centres are formed 7 to become the carpal bones, 2 to become the distal epiphyses of the radius and ulna, and 19 at the sites of the epiphyses of the metacarpal and phalangeal bones. The adductor sesamoid

Fig 4

X-ray film of hand and wrist which shows, according to Greulich & Pyle's atlas, skeletal age 9 years for boys and skeletal age $7^{10}/_{12}$ years for girls.



F g 5

X-ray film of hand and wrist which shows, ccording to Greulich & Pyle tlas, k letal ge approx. 12 years for boys and skeletal age 10 years f girls

Fig. 6

X-ray film of hand and wrist which shows, according to Greulich & Pyle atlas, skeletal age 14 years for boys and skeletal age 12 years for girls.

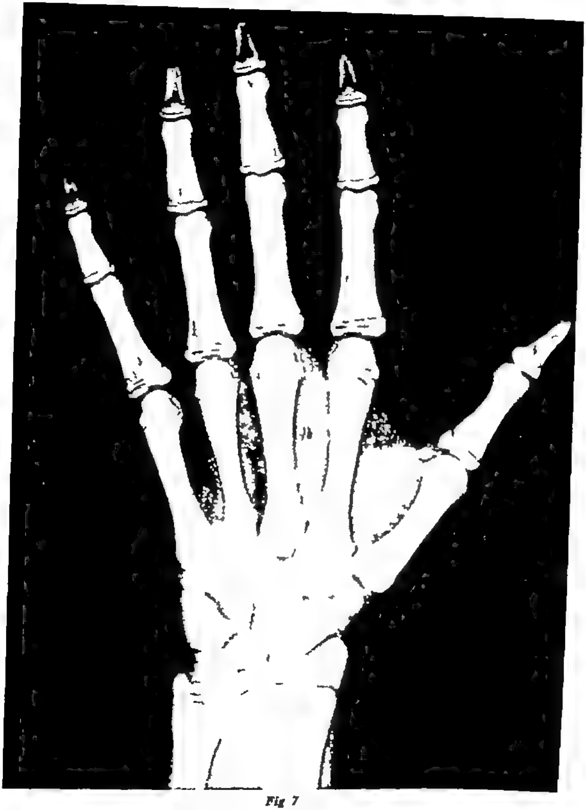


Fig 7

X ray film of hand and wrist which shows, according to Greulich & Pyle skeletal age 15 years for boys and skeletal age 13 years for girls

Fig 8

X-ray film of hand and wrist which shows, according to Greulich & Pyle atlas, skeletal ag[e] 15[1] years for boys and skeletal age 13[1]/[2] years for girls.

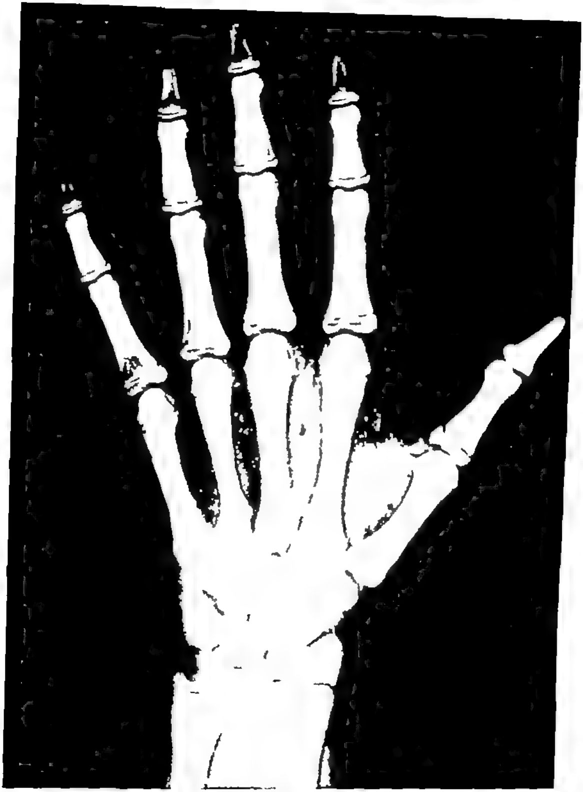


Fig 7

X-ray f lm of hand and wrist which shows accord g to Greulich & Pyle tlas, skeletal ge 15 years for boys and sk letal age 13 years for girls.

Fig 8

X-ray film of hand and wrist which shows, according to Greulich & Pyle atlas, skeletal age 15 years for boys and skeletal age 13½ years for girls.

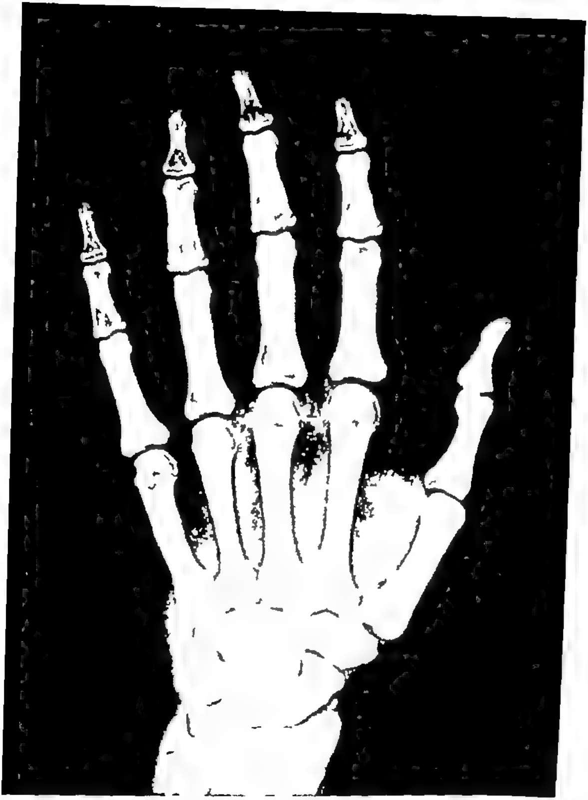


Fig 9

X ray film of hand and wrist which shows, ccording t Greulich & Pyle tlas, k letal age 16 years for boy and skeletal age 14 years for girls.

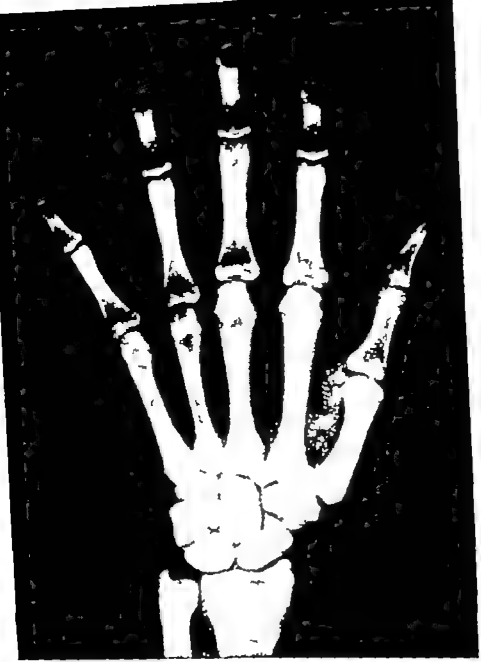


Fig 10

X-ray film of hand and wrist which shows, according to Greulich & Pyle atlas, skeletal age 17 years for boys and skeletal age 15 years for girls.

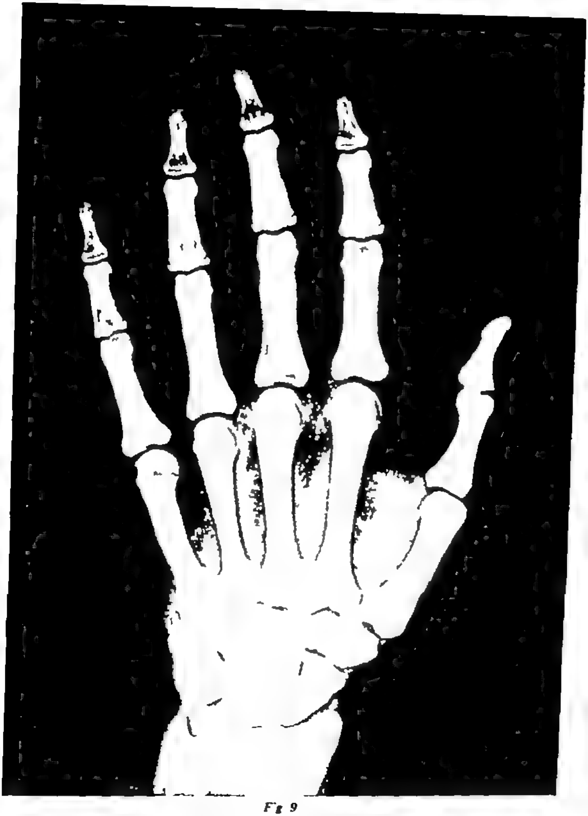


Fig 9

X ray film of hand and wrist which shows, according to Greulich & Pyle tlas, k letal g
16 years for boy and skeletal age 14 years for gi ls.

Table 2

Ages of onset and completion, and the span of development of 29 ossification centres of the hand and wrist (Stuart, Pyle, Cornoni & Reed)

Girls.

Bone	Mean onset, order	Number	Onset		Completion		Span	
			M	SD	M	SD	M	SD
Capitate	1	53	2.5	1.8	159	10	157	10
Hamate	2	53	3.1	2.2	159	10	156	10
Radius	3	44	10.0	4.1	200	12	190	12
Finger 3 prox. phal. epiph.	4	56	10.6	3.2	166	12	155	11
Finger 2, prox. phal. epiph.	5	56	10.9	2.9	166	12	155	11
Finger 4 prox. phal. epiph.	6	56	11.0	3.2	166	12	155	11
Metacarpal 2, epiph.	7	53	13.1	3.3	170	13	156	13
Finger 1 distal phal. epiph.	8	56	13.2	3.5	157	11	144	10
Metacarpal 3 epiph.	9	53	14.4	3.9	170	13	156	13
Finger 5, prox. phal. epiph.	10	56	14.7	3.8	164	12	150	11
Metacarpal 4, epiph.	11	53	15.5	3.8	169	14	153	14
Finger 3 middle phal. epiph.	12	56	15.7	3.4	167	12	152	11
Finger 4 middle phal. epiph.	13	55	16.0	3.2	168	12	152	11
Finger 2, middle phal. epiph.	14	56	17.0	3.4	166	12	149	11
Metacarpal 5 epiph.	15	53	17.0	3.0	170	13	153	12
Triquetral	23	55	26.6	14.0	160	9	133	15
Finger 3 distal phal. epiph.	16	57	19.1	6.0	159	11	140	11
Finger 4 distal phal. epiph.	17	57	19.6	5.9	159	12	139	11
Metacarpal 1 epiph.	18	55	19.9	3.4	164	13	144	12
Finger 1 prox. phal. epiph.	19	57	21.6	6.4	165	11	144	11
Finger 2, distal phal. epiph.	20	57	23.0	6.8	156	11	133	11
Finger 5, distal phal. epiph.	21	57	23.0	6.7	160	13	135	13
Lunate	24	55	36.1	17.3	160	9	124	16
Finger 5, middle phal. epiph.	22	55	23.9	8.3	165	12	139	12
Navicular	27	54	53.7	13.8	160	9	106	13
Lesser multangular	26	55	51.8	12.3	160	9	108	13
Greater multangular	25	54	51.6	16.4	160	9	108	[illegible]
Ulna	28	51	72.4	12.1	191	12	119	12
Adductor sesamoid (thumb)	29	47	127.8	10.3	167	14	39	13

Means (M) and standard deviations (SD) are expressed in months

of the thumb does not form until towards puberty. The sequence in which the ossification centres appear differs significantly from that in which bone formation is completed (Stuart, Pyle, Cornoni & Reed).

The maturation of the hand and wrist bones is completed, according to Table 1, in boys roughly in the following sequence and at the following times: carpal bones $15^{8}/_{12}$ years, distal phalanges $15^{9}/_{12}$ years, proximal and middle phalanges $15^{11}/_{12}$ years, metacarpal bones $16^{7}/_{12}$ years, and radius 17 $/_{12}$ years.

The maturation of the same bones in girls is completed as follows (Table 2): distal phalanges $13^{2}/_{12}$ years, carpal bones $13^{3}/_{12}$ years, proximal phalanges $13^{9}/_{12}$ years, middle phalanges

Fig 11

X-ray film of hand and wrist showing the final hand skeleton.

Table 2

Ages of onset and completion, and the span of development of ossification centres of the hand and wrist (Stuart, Pyle, Cornoni & Reed)

Girls.

Bone	Mean onset, order	Number	Onset M	Onset SD	Completion M	Completion SD	Span M	Span SD
Capitate	1	55	2.5	1.8	159	10	157	10
Hamate	2	55	3.1	2.2	159	10	156	10
Radius	3	44	10.0	4.1	200	12	190	12
Finger 3 prox. phal. epiph.	4	56	10.6	3.2	166	12	155	11
Finger 2, prox. phal. epiph.	5	56	10.9	2.9	166	12	155	11
Finger 4 prox. phal. epiph.	6	56	11.0	3.2	166	12	155	11
Metacarpal 2, epiph.	7	55	13.1	3.5	170	13	156	13
Finger 1 distal phal. epiph.	8	56	13.2	5.5	157	11	144	10
Metacarpal 3, epiph.	9	55	14.4	3.9	170	13	156	13
Finger 5 prox. phal. epiph.	10	56	14.7	3.8	164	12	150	11
Metacarpal 4 epiph.	11	55	15.5	3.6	169	14	153	14
Finger 3, middle phal. epiph.	12	56	15.7	5.4	167	12	152	11
Finger 4 middle phal. epiph.	13	55	16.0	5.2	168	12	152	11
Finger 2, middle phal. epiph.	14	56	17.0	4	166	12	149	11
Metacarpal 5, epiph.	15	55	17.0	5.0	170	13	153	12
Triquetral	23	55	26.6	14.0	160	9	133	15
Finger 3, distal phal. epiph.	16	57	19.1	6.0	159	11	140	11
Finger 4 distal phal. epiph.	17	57	19.6	3.9	159	12	139	11
Metacarpal 1 epiph.	18	55	19.9	5.4	164	13	144	12
Finger 1 prox. phal. epiph.	19	57	21.6	6.4	165	11	144	11
Finger 2, distal phal. epiph.	20	7	23.0	6.8	158	11	133	11
Finger 5, distal phal. epiph.	21	57	23.0	6.7	160	13	135	1
Lunate	24	55	36.1	17.3	160	9	124	16
Finger 5 middle phal. epiph.	22	55	25.9	8.3	165	1	139	12
Navicular	27	54	53.7	13.8	160	9	106	15
Lesser multangular	26	55	51.8	12.3	160	9	108	13
Greater multangular	25	54	51.6	16.4	160	9	108	18
Ulna	28	51	7..4	12.1	191	12	119	13
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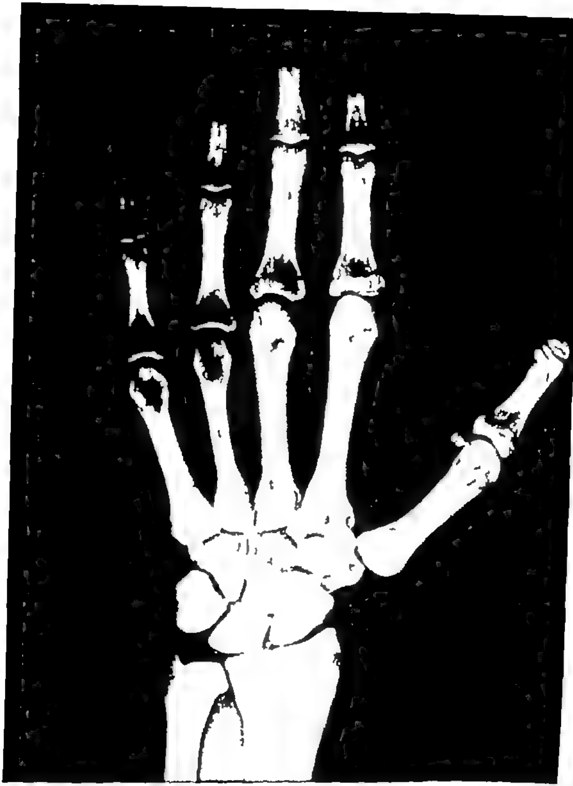
The maturation of the hand and wrist bones is completed, according to Table 1 in boys roughly in the following sequence and at the following times carpal bones $15^{9}/_{12}$ years, distal phalanges $15^{10}/_{12}$ years, proximal and middle phalanges $15^{11}/_{12}$ years, metacarpal bones $16^{3}/_{12}$ years, and radius $17^{4}/_{12}$ years.

The maturation of the same bones in girls is completed as follows (Table 2) distal phalanges $13^{7}/_{12}$ years, carpal bones $13^{9}/_{12}$ years, proximal phalanges $13^{9}/_{12}$ years, middle phalanges



F g 11

X ray film of hand and wrist showing the final hand sk leton

61 % of the boys showed a sequence of ossification as described by Greulich & Pyle (1959) This may presumably be explained largely by the fact that the children of this study were from the lower middle class, whereas the children of Greulich & Pyle s material were in the best conceivable social environment.

Garn & Rohmann (1960 a) set up their own ossification sequence. On comparison with Greulich & Pyle s (1959) Pyle & Sontag's, and Stuart & Stevenson s they found a high positive correlation between the various sequences (coefficient of correlation 0.9)

Finding a high correlation between the appearance of the various round bones as well as between the appearance of the epiphyses of the short bones, Robinow suggested that in assessing skeletal maturity the skeletal age of the round as well as of the short bones should be determined.

The fact that skeletal maturation takes place according to a fairly well-defined pattern has inspired the setting up of various systems for determining skeletal age. The maturation process is roughly concurrent in all parts of the skeleton. Some authors have preferred letting the bones of the hand represent skeletal development, while others have studied skeletal maturation in the foot, knee, or hip. Finally one side of the entire skeleton has been used in working out a system for assessing skeletal age.

Below a number of these studies will be reviewed, giving most attention to the two systems which were used as a basis for comparison in the present study Thereafter a number of older and more recent studies will be briefly mentioned.

Systems for Assessing Skeletal Age Based Upon Ossification Centres in the Hand and Wrist

T W Todd's Atlas

In 1926 T W Todd, Western Reserve University School of Medicine, Cleveland, Ohio, started a longitudinal study of unselected children from a school. During the first year the study comprised 800 children, during the second year 400 during the third year 200 during the fourth year 85 fifth year 45 sixth year 25 and seventh year 15 This experiment was carried through, but when Todd observed the trend, he felt that a study of selected children would be preferable.

In 1931 Todd started a comprehensive, accurately planned survey on the growth and development of normal children and worked on this project until his death in 1938 Thereafter it was continued, in charge of W W Greulich, and was completed in 1942 as originally planned by Todd. The expenses of the entire project were defrayed by the Brush Foundation, and it is usually known as the Brush Foundation study Concurrently with the study of the selected Brush Foundation children, Todd carried out several cross-sectional studies of children from a socially poorer environment.

Selection of Children. A total of 4500 children were included. They had been selected by paediatricians who had

$13^{10}/_{12}$ years, metacarpal bones $14^{2}/_{12}$ years, and radius $16^{8}/_{12}$ years. These figures are the results of a longitudinal study of 66 boys and 67 girls performed in the *Harvard School of Public Health* during the period 1930–1956 The children were born in a Boston hospital, they were healthy and their parents were of Northern European descent. Otherwise, there was no special selection.

The period which elapses from the first until the last epiphysis in the hand closes varies from 1 to 4 years (Garn Rohmann & Apfelbaum) Lavine, Moss & Noback (1962) found this span to vary from 4 to 28 months. They X rayed 111 children every 3 months from the age of 9 to 16 years. Garn et al. X rayed the children only every 6–12 months, and this may well be the explanation why they found a wider range.

Chronological Difference in the Skeletal Maturation of Boys and Girls

Ossification centres appear earlier in girls than in boys. Pryor (1923) found the difference in skeletal maturation between the two sexes to be days during foetal life, months during the first years of life, and years during puberty These phenomena are apparent from Tables 1 and 2 The capitate and hamate bones, which appear during the first year of life, develop 2–4 weeks earlier in girls than in boys. The completion of the carpal, phalangeal and metacarpal bones occurs about 2 years earlier in girls than in boys.

It is apparent also from Tables 1 and 2 that the standard deviations of the onset, completion, and span of ossification are less for girls than for boys.

Sequence of Ossification

The ossification centres appear in a well-defined sequence, almost the same for boys and for girls (Pryor 1907 Greulich & Pyle 1959 Pyle, Stuart Cornoni & Reed Stuart, Pyle, Cornoni & Reed)

Pryor (1907) described various deviations from the usual sequence, but on analysing Pryor s material Greulich (1959) found that these deviations were mostly explicable by disease or poor social conditions.

The sequence in which the ossification centres appear is presumably genetically determined, the same deviations from the most common sequence of ossification being manifest within the same families (Pryor 1907 Reynolds 1943 Reynolds & Schoen 1947)

Snodgrasse et al. (1955) found a significantly larger number of abnormalities in the maturation of the hand skeleton among children with nutritional disturbances than among healthy children. Irregularities in the sequence of ossification are most common in the carpal bones, cf the higher standard deviations for ossification of the carpal bones than for ossification of the epiphyses (Tables 1 and 2) Garn & Rohmann (1960 b) studied the variability in the order of ossification in the hand Studying 2880 X ray films of 154 children in a longitudinal study they found that only 49 % of the girls and

61 % of the boys showed a sequence of ossification as described by Greulich & Pyle (1959) This may presumably be explained largely by the fact that the children of this study were from the lower middle class, whereas the children of Greulich & Pyle s material were in the best conceivable social environment.

Garn & Rohmann (1960 a) set up their own ossification sequence. On comparison with Greulich & Pyle s (1959) Pyle & Sontag's, and Stuart & Stevenson s they found a high positive correlation between the various sequences (coefficient of correlation 0 9)

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Selection of Children. A total of 4500 children were included. They had been selected by paediatricians who had

made sure that the children were not suffering from any physical or mental defects. The parents had given their permission for the children to take part in the project until it was finished In other words, this was a longitudinal survey

The criteria in respect to the parents, for including the children in the project were that the parents were interested in their children's physical well-being and mental development and that they took the time to act in accordance with this attitude

All the included children were from homes which were above the average educational and economic level but this had not been a condition All the children were white, of Northern European descent

The investigation comprised children in the age range 3 months to 19 years. During the first year of life the children were examined at 3-month intervals, later every 6 months. The examination consisted in X raying the left hand elbow shoulder foot, knee, and hip. Furthermore, measurement of height and other anthropometric measurements, i.e. of sitting height, arm length leg length circumference of skull, circumference of chest, and weighing Psychological tests were done, and the parents were questioned about the child's health since the last examination

Selection of Standards. Todd studied the skeletal maturation in all 6 above mentioned skeletal areas, but gave most attention to that of the hand skeleton

X rays of the hand skeleton were grouped by chronological age. Within each group the films were arranged in order according to the stage of maturity and the film which was most representative of the group was selected as a standard for the chronological age concerned. (Todd and his associates had previously studied the development of the hand skeleton on the films from the school study and found that for each individual bone the various indicators of maturity always appeared in the same sequence) Todd performed this selection of standards several times, first on the basis of the films from the 1926 school study later in 1931 and 1934 on the basis of films from the cross-sectional surveys, and finally in 1935 on the basis of films from the Brush Foundation study The last mentioned standards showed earlier skeletal maturation, explicable by the better social circumstances in which the children of the Brush Foundation study were raised.

Todd's Atlas of Skeletal Maturation of the Hand published in 1937 was based upon films of 1000 children of the Brush Foundation study and also upon films from the cross-sectional studies of children from a socially poorer environment. The standards for children during puberty were based almost exclusively upon films from the cross-sectional studies.

Greulich & Pyle's Atlas

After the investigation had been completed in 1942 Greulich & Pyle worked out a new atlas (1950) on the maturation of the hand skeleton according to the lines laid down by Todd However

they used exclusively films of children from the Brush Foundation study Each standard was selected from among 100 children of the same age and sex.

Whenever possible, films of the same child were used for successive standards. However the most representative film from the group was selected even though this interfered somewhat with the continuity from standard to standard. In 1959 they published a revised edition of the atlas which contained, for the boys, 2 extra standards for the ages 12 1/2 and 19 1/2 years and in which the standard for the age 13 1/2 years was replaced by a standard for the age 13 years. The 1959 edition was used in the present investigation.

The atlas gives, up to the age of 1 year standards for every 3 months, from the age of 1 to 5 years for every 6 months, and thereafter for each whole year For the time around puberty when maturation is faster a few extra standards have been inserted. This makes the time intervals between the standards somewhat irregular but the maturation is illustrated in a series of more continuous films. Figs. 4–11 show from the present material, examples of various stages of skeletal maturation. Each of the figures has been assessed on the basis of Greulich & Pyle's atlas, partly by the boys' and partly by the girls standards.

Use of the Atlas. When assessing the skeletal maturity of a child's hand, the standard which corresponds to the child's age and sex is looked up, and the film is compared with the standard concerned as well as with the standards for the ages just below and just above. In early childhood the comparison is based mainly upon the presence of the carpal bones. During puberty the thing to be considered is fusion of the epiphyses with the shafts, and at intermediate ages the comparison is done mainly by assessing the shape and mutual size of the bones.

In fact, the standards are directly applicable only for the material used in working out the atlas, as racial and environmental differences may influence skeletal maturation.

Greulich & Pyle's atlas gives for each picture a number of maturity indicators, i.e. descriptions of characteristic changes in the shape and fusion of the individual bones. These maturity indicators form the basis of a more detailed determination of skeletal age, each bone and epiphysis being assessed separately The atlas gives for each bone a skeletal age, if it is estimated to differ from the age of the entire standard.

Greulich himself assessed the skeletal age of children from the Brush Foundation study 60 children from each age group. He found that the mean standard deviation for boys in the age range 7–17 years was 11.0 months, i.e. that about two-thirds of the boys are of a skeletal age deviating by ± 11.0 months or less from the standard with which they ought to comply according to their age. One-third deviated by more than ± 11.0 months. As far as the girls are concerned, the mean standard deviation was ± 10.3 months. Greulich & Pyle (1959) mentioned that Stuart had studied the skeletal age of 50–60 children of each age group and sex in

made sure that the children were not suffering from any physical or mental defects. The parents had given their permission for the children to take part in the project until it was finished. In other words, this was a longitudinal survey

The criteria, in respect to the parents, for including the children in the project were that the parents were interested in their children's physical well-being and mental development and that they took the time to act in accordance with this attitude.

All the included children were from homes which were above the average educational and economic level but this had not been a condition All the children were white, of Northern European descent

The investigation comprised children in the age range 3 months to 19 years. During the first year of life the children were examined at 3-month intervals, later every 6 months. The examination consisted in X raying the left hand, elbow shoulder foot knee, and hip. Furthermore, measurement of height and other anthropometric measurements, i.e. of sitting height, arm length leg length circumference of skull circumference of chest, and weighing Psychological tests were done, and the parents were questioned about the child's health since the last examination.

Selection of Standards Todd studied the skeletal maturation in all 6 above-mentioned skeletal areas, but gave most attention to that of the hand skeleton

X rays of the hand skeleton were grouped by chronological age. Within each group the films were arranged in order according to the stage of maturity and the film which was most representative of the group was selected as a standard for the chronological age concerned. (Todd and his associates had previously studied the development of the hand skeleton on the films from the school study and found that for each individual bone the various indicators of maturity always appeared in the same sequence) Todd performed this selection of standards several times, first on the basis of the films from the 1926 school study later in 1931 and 1934 on the basis of films from the cross-sectional surveys, and finally in 1935 on the basis of films from the Brush Foundation study The last mentioned standards showed earlier skeletal maturation, explicable by the better social circumstances in which the children of the Brush Foundation study were raised.

Todd's Atlas of Skeletal Maturation of the Hand published in 1937 was based upon films of 1000 children of the Brush Foundation study and also upon films from the cross-sectional studies of children from a socially poorer environment The standards for children during puberty were based almost exclusively upon films from the cross-sectional studies.

Greulich & Pyle's Atlas

After the investigation had been completed in 1942 Greulich & Pyle worked out a new atlas (1950) on the maturation of the hand skeleton according to the lines laid down by Todd However

Kopczynska, therefore suggested working out standards for each country and pointed out that when skeletal age was assessed by foreign standards, the findings should be corrected on the basis of national standards.

J M Tanner & R H Whitehouse's System for Assessing the Maturity of the Hand Skeleton

A British method of assessing the maturity of the hand skeleton (Tanner & Whitehouse 1959 Tanner Whitehouse & Healy 1962) has been accessible in its present form since 1962.

Survey of the Working Out and Application of the Method For each individual bone of the hand and wrist Tanner & Whitehouse drew and described a number of maturity stages (cf. examples in Figs. 12–16) The drawings were made on the basis of a number of longitudinal X ray studies, especially of children from an orphanage near London. This project has so far been in progress for more than 10 years and is known as the Harpenden Growth Study

The number of maturity stages was reduced to 9 for the radius and to 8 for the other bones. The stages were arbitrary stages in the maturation from birth until the hand skeleton had completed its growth. The stages are denoted by letters, not ciphers, to avoid giving the impression that the stages are equally spaced.

For each stage of each bone 1 2, or praised girls and boys ranging in age from 1 month to 16 years.

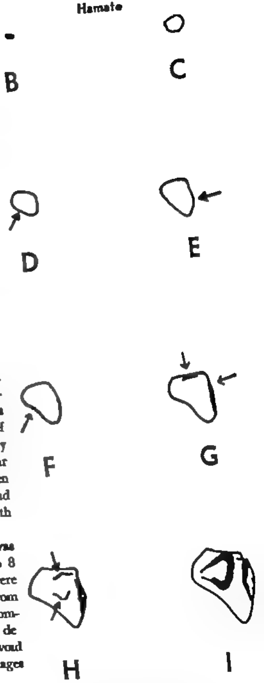

Fig 13

Stages in the maturation of the hamate from the appearance of the bone until its final stage. (Tanner & Whitehouse 1962)

Boston. He found that on the average the boys were retarded 2 months in relation to the children of the Brush Foundation study and that the mean standard deviation was 12.0 months. The girls were retarded by an average of 3 months, and the SD was 11 3 months.

It will be seen from Chapter 14 which deals with the influence of social factors upon skeletal maturation that Sutow (1952) used Greulich & Pyle's atlas *for assessing the skeletal maturation of Japanese children. Greulich* (1951) used the same atlas in a study of the skeletal maturation of school children on the isle of Guam, in a study of the skeletal development in American-born Japanese in the environs of San Fransisco (Greulich 1957) and in the study of Greulich et al (1953) of the skeletal age of Japanese children who had been exposed to the atomic bombing in Hiroshima.

In a cross-sectional study of 12 000 Polish boys and girls aged 7–16 years Kopczynska (1964) assessed the skeletal age by the Greulich & Pyle atlas method and related it to sex, height, weight, and social status. The skeletal maturation in the Polish children showed a pattern different from that in the American children upon whom Greulich & Pyle's atlas was based. The Polish girls aged 7–10 years showed the same *skeletal maturation as the* American ones, but older Polish girls were skeletally more advanced. The Polish boys, except for those who were 14 and 15 years of age, showed a retarded skeletal maturation. The difference between skeletal age and chronological age varied from age to age.

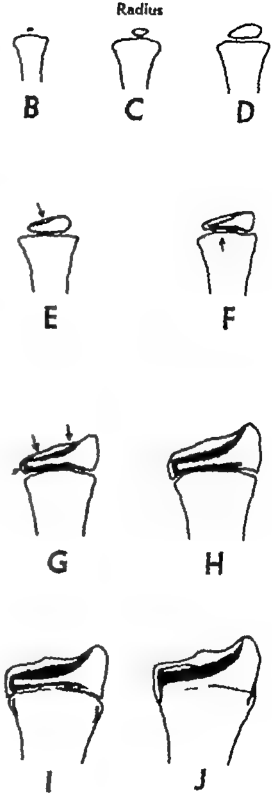

Fig 1

Stages in the maturation of the radius from the appearance of the bone until its final stage (Tanner & Whitehouse 1962)

Kopczynska, therefore, suggested working out standards for each country and pointed out that when skeletal age was assessed by foreign standards, the findings should be corrected on the basis of national standards.

J. M. Tanner & R. H. Whitehouse's System for Assessing the Maturity of the Hand Skeleton

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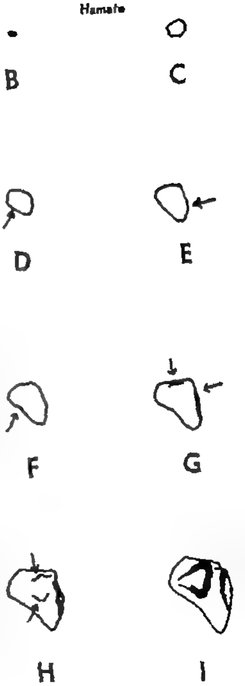

Fig. 13

Stages in the maturation of the hamate from the appearance of the bone until its final stage. (Tanner & Whitehouse 1962).

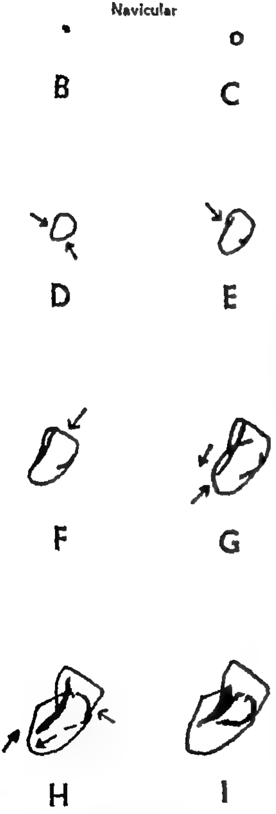

Fig 14

Stages in the maturation of the navicular from the appearance of the bone until its final stage (Tanner & Whitehouse 1962)

3 criteria have been described If only *one criterion is* given it has to be met if the bone is to be assessed as having reached the stage concerned If 2 criteria are given only one has to be met If 3 criteria are given 2 have to be met if the bone is to have reached the stage concerned Before a bone can be said to have reached a given stage, the first stated criterion of the preceding stage must also have been satisfied. The descriptions of the criteria are supplemented by drawings.

The criteria include the following factors (1) presence or absence of ossification centres, (2) closure of epiphyses, (3) relative sizes of ossification centres and relative distances between bones, (4) whether or not the bones are in contact and if so whether the contact is at a point or along a surface The measurements of item (3) sometimes require the use of a simple pair of dividers.

Scores were given for each developmental stage for each bone 0 when the ossification centre was not yet visible and 100 when the bone had reached its final stage

The score for the intermediate stages was calculated in such a way that the total score for the bones was given minimum variance for the individual hand According to this preliminary rating system a hand in the final stage attained 2800 the hand and wrist consisting of 28 bones and sesamoid bones. The calculations concerning the rating were based upon a cross-sectional study of about 2600 British children of 6 groups believed to be representative of an average socio-economic level in the British population This material [illegible]

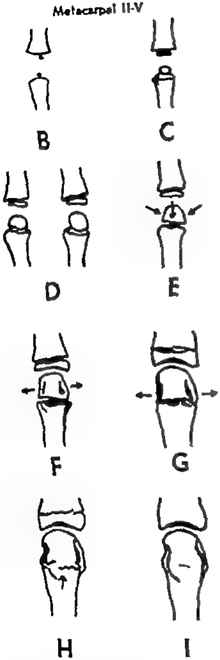

Fig. 1

Stages in the maturation of the 2nd–5th metacarpals from the appearance of the head of the metacarpal until its fusion with the diaphysis. (Tanner & Whitehouse 1962)

It was endeavoured to assess whether it was justified to let all bones contribute an equal share to the total skeletal age, but this problem could not be solved by statistical calculations on the correlations between the bones.

On the basis of purely biological considerations, it was then necessary to form an estimate of how the bones were to be combined—according to their role in the development of the entire hand skeleton.

The biological considerations were that a simple average of all the bones would be overweighted by the large number of metacarpal and phalangeal bones which develop almost simultaneously and in approximately the same way. Therefore, metacarpal bones 2 and 4 and the corresponding phalangeal bones were left out of the system which then included 20 bones

radius, distal epiphysis
ulna, distal epiphysis
metacarpal I, III and V
proximal phalanx I, III, and V
middle phalanx III and V
distal phalanx I III and V
capitate
hamate
triquetral
lunate
navicular
greater multangular
lesser multangular

As it was presumed that the development of the long and of the round bones was controlled by different factors, the rating system was worked out in the way that these two sets of bones

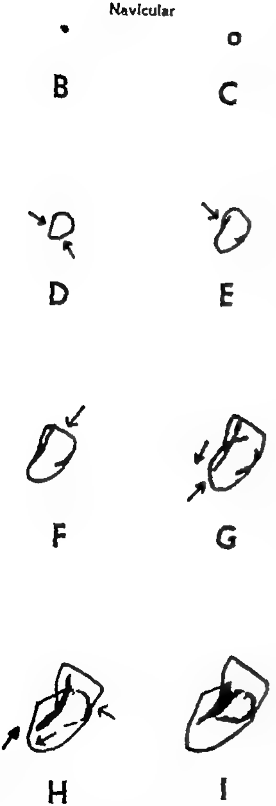

Fig 14
Stages in the maturation of the navicular from the appearance of the bone until its final stage (Tanner & Whitehouse 1962)

3 criteria have been described. If only one criterion is given it has to be met if the bone is to be assessed as having reached the stage concerned. If 2 criteria are given only one has to be met. If 3 criteria are given 2 have to be met if the bone is to have reached the stage concerned. Before a bone can be said to have reached a given stage, the first stated criterion of the preceding stage must also have been satisfied. The descriptions of the criteria are supplemented by drawings.

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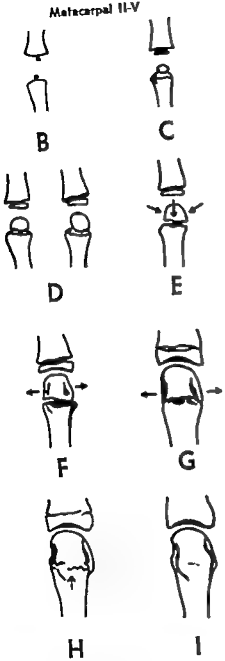

Fig 15

Stages in the maturation of the 2nd-5th metacarpals from the appearance of the head of the metacarpal until its fusion with the diaphysis. (Tanner & Whitehouse 1962)

It was endeavoured to assess whether it was justified to let all bones contribute an equal share to the total skeletal age, but this problem could not be solved by statistical calculations on the correlations between the bones.

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The biological considerations were that a simple average of all the bones would be overweighted by the large number of metacarpal and phalangeal bones which develop almost simultaneously and in approximately the same way. Therefore, metacarpal bones 2 and 4 and the corresponding phalangeal bones were left out of the system which then included 20 bones

radius, distal epiphysis
ulna, distal epiphysis
metacarpal I III and V
proximal phalanx I III, and V
middle phalanx III and V
distal phalanx I III, and V
capitate
hamate
triquetral
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navicular
greater multangular
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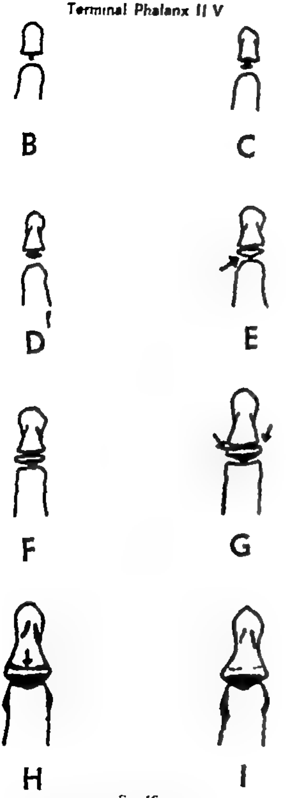


Fig 16

Stages in the maturation of the distal phalanges II–V from the appearance of the epiphysis until its fusion with the diaphysis (Tanner & Whitehouse 1962)

contributed 50 % each to the score in the mature hand skeleton, and so that each set of bones may be assessed separately by some conversions. Thus, the 7 carpal bones each contribute by approx 7 % of the development of the entire hand the ulna and radius each by 10 % and the 1st 3rd and *5th metacarpal bone with corresponding* phalangeal bones each by 10 %

In the assessment of the skeletal age of a hand, the maturity stages of the 20 named bones are estimated Each stage is rated according to a scoring system worked out according to the above mentioned lines. The scores are added and looked up in a table (listing scores from 0–1000) which converts the scores to skeletal ages. The scale closes as far as the boys are concerned at a skeletal age of 18 years and for the girls at 17 years.

Since, however the material comprises only children up to the age of 16 years, and since the named limits were fixed, the scale is inaccurate for the oldest age groups, as also pointed out by Tanner & Whitehouse.

When the scores are converted to a log scale, the diagrams show rapid growth in the youngest age groups, slower from 7 to 10 years of age, rapid around puberty and then again slow

Plotting skeletal ages against chronological ages gives a rectilinear course of the curve, and the percentiles run parallel with this line from about 5 years of age and onwards. The distance between the 10 % and 90 % percentile for a given chronological age may be read from the curve as about 32 months. This corresponds to a SD of 12–12 5 months.

Other Studies of the Maturation of the Hand Skeleton

Behrendsen (1897) and *Ranke* (1898) published X rays of the hand skeleton of boys and girls of various ages, described the changes in development from age to age, and pointed out that the number of ossification centres in the hand skeleton seen by X-rays express roughly the child's age.

Holmgren (1910) from X-rays of the hands of 115 children with Graves disease, compared the skeletal maturity with reported findings concerning the time of epiphyseal fusion with the diaphyses. He concluded that the children of his study showed very early maturation.

In 1921 *Stettner* published a paper on the normal and abnormal development of the hand skeleton. He related skeletal maturity to height, sex, and social circumstances. The study showed that children from rural districts were skeletally retarded compared with children from urban areas. He confirmed the marked variation in the times of appearance of the individual ossification centres.

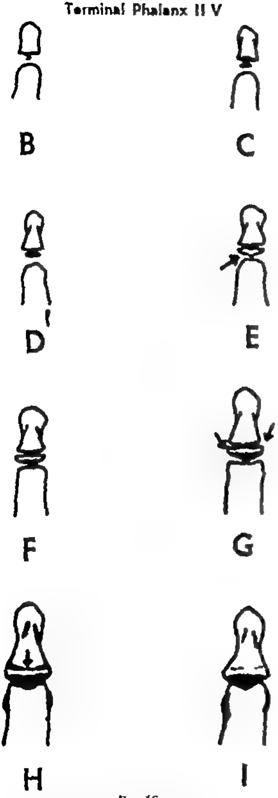
Siegert's "Atlas der normalen Ossifikation der menschlichen Hand" was published in Germany in 1935. This was the first atlas to illustrate the maturation of the hand skeleton. He made a single examination by X-ray of each of 244 girls and 200 boys who were carefully selected for a cross-sectional study. He found the sequence in which the bones ossify to be fairly regular and similar in both sexes and ossification to occur earlier in girls than in boys. The atlas comprised 130 X-rays out of a total of 444. Thus, in fact this atlas is a number of case reports demonstrating the skeletal maturation from 0 to 12 years. Siegert believed that a given stage of maturity in a normal child corresponded to a given age. Todd on the other hand realized that there are normal variations which may be described by mean values with standard deviations.

Flory's Atlas

Flory in 1936, published an atlas of the maturation of the hand skeleton. He used 5000 X-rays taken in a mixed longitudinal cross-sectional study of children aged 5–17 years from the Chicago Laboratory School. These children were above average in intelligence as well as in respect to parents income and social status. In addition, the material included 300 X rays of children aged 0–5 years from 2 Chicago hospitals and 225 X-rays of adolescents aged 18–20 years from the University of Chicago, Junior College.

It had first been Flory's intention to employ planimetry of the bones in the carpal region for working out a system for estimating skeletal maturation. However after having consulted with Todd in 1931 he altered his method and used, like Todd, the Inspection method. He selected his standards by the same pattern as Todd choosing from among 100 X-rays of children of the same age and sex, the film which best represented the average as a standard. The standards were accompanied by descriptions including the same criteria which Todd had suggested.

Flory demonstrated that the correlation between physical maturity and



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technically poor. As there is a 1 year interval between the standards after the age of 4 years, there are too few films to show the rapid development during puberty.

Systems for Assessing Skeletal Age Based Upon Ossification Centres in the Foot, Knee or Hip

The large material from the Brush Foundation study was further utilized when *Pyle & Hoerr* (1955) published an atlas of the *skeletal maturation of the knee*.

As a further result of the same comprehensive study *Hoerr, Pyle & Francis'* atlas of *skeletal maturation of the foot and ankle* appeared in 1962. This atlas differs from the hand atlas in having only a single set of standards common to boys and girls. With each standard the skeletal ages are given for boys and girls respectively. As in Greulich & Pyle's atlas maturity indicators are described for each bone. Much earlier Bade (1899) and Hasselwander (1903) had described the maturation of the foot skeleton during foetal life and early childhood. Both pointed out marked variations in the times of appearance of the individual ossification centres.

In 1937 *Acheson* published his study on *skeletal maturation of the hip*. His method was derived from the study of 6500 X-rays from the Brush Foundation study and of 6000 X-rays of children from the Institute of Social Medicine, Oxford, England, and is called the Oxford method.

For each ossification centre in the hip Acheson listed a number of maturity indicators, i.e. definitions of easily demonstrable changes in the shape and degree of fusion of the bones. He rated the individual ossification centres according to the stage of maturation they had reached and worked out a table which expresses, in percentages for a given overall score, the maturation of the hip concerned.

This method has the advantage that indicators appear in the hip over a large number of years. For instance, during the first 6 months of life a larger number of indicators appear in the hip than in any other part of the skeleton, and new indicators continue to appear after other parts of the skeleton have reached their final stage.

The drawbacks of the method are that the study involves irradiation of the gonads and that the reading of the X-rays is time-consuming and requires some experience.

The accuracy in reading the films is the same with Greulich & Pyle's method as with the Oxford method, there being no significant difference between the correlation coefficients for age and skeletal maturity by the two methods. Acheson recommends Greulich & Pyle's atlas for clinical use, but feels that the Oxford method is preferable for research purposes, because it has its own scale.

System for Assessing Skeletal Age Based Upon Ossification Centres in Half the Peripheral Skeleton

In 1964 *Elgenmark*, in Sweden, published a study of the *normal maturation of the ossification centres in children aged 1 month to 5 years.*

skeletal age is highest when the skeletal age is measured by the inspection method (*atlas method*) *less marked* when measuring the ossification ratio (the relation between the length and width of various bones) and least in the planimetry method The reason why the estimation of skeletal age is less accurate when it is determined by the ossification ratio or by planimetry *is presumably* that these methods do not contain criteria for differentiation. These methods are least accurate during the years of and after puberty

However Flory's material was heterogeneous, *it is not sufficiently described*, his X rays are technically poor and the hand is incompletely shown in some of the exposures.

In 1950 *Speijer* in Holland, published an atlas on the maturation of the hand skeleton He had performed a cross-sectional study of a total of *360 healthy children in Leiden. The* material comprised 10 boys and 10 girls for each year of age from 3 to 20 years and was drawn from nursery and other schools as well as students and apprentices.

The left hand and hip were X rayed. For each group of 10 he chose the picture which was judged the best representative of the group and also those which showed the most advanced and the most retarded skeletal maturation. Thus, for each chronological age *Speijer presented 3 X rays to demon*strate the degree of maturity and variations thereof Comparing the X rays for the different ages, *he found that* for boys in the age range 3–9 years there was a normal variation of ± 2 years, in the age range 9–14 years a variation of ± 4 years, and at higher ages again a variation of ± 2 years. *As far as the girls were concerned, the* variation was said to be fairly constant at ± 2 years.

The material is small and could not be analysed statistically No other investigators have attempted to test the method, and the quality of the X rays is not particularly good.

In 1960 the German authors *Schmid & Moll* published their atlas on the normal and abnormal development of the hand skeleton. This atlas was worked out on the basis of a cross-*sectional study of 4000 children aged* 0–14 years, half of whom were healthy Up to the age of 1 year the children were *divided* into age groups *of 3* months, from 1–4 years into age groups of 6 months, and thereafter into age groups of 12 months.

On each film measurements were *made by planimetry of the epiphyses* of the carpal bones, the distal epiphyses of the ulna and radius, and the epiphysis of the 1st metacarpal bone.

The atlas presents for each group the average example together with the most advanced and most retarded ones. The means, standard errors, and standard deviations are tabulated. Schmid & Moll maintain that the planimetry method shows a negligible difference in maturation of boys and girls and therefore give only one set of standards. The planimetry method does not reveal the time difference in maturation of up to 2 years between girls *and boys, and* Schmid & Moll do not take this difference into account Therefore, the method must be inaccurate. The pictures *in the atlas are*

technically poor As there is a 1 year interval between the standards after the age of 4 years, there are too few films to show the rapid development during puberty

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System for Assessing Skeletal Age Based Upon Ossification Centres in Half the Peripheral Skeleton

In 1964 *Elgenmark* in Sweden, published a study of the *normal maturation of the ossification centres in children aged 1 month to 5 years*.

He wanted to elucidate the time of appearance of the various ossification centres in Swedish children. His material comprised 429 boys and 423 girls from Stockholm and environs, selected among children who had been examined or treated at the paediatric hospital "Samariten" in Stockholm. All the children were healthy and in good nutritional state. A small proportion were examined several times. The study was planned as a cross-sectional survey. The children were divided into 1 month groups up to 1 year of age and thereafter into 3 month groups.

The investigation consisted in X-raying the left half of the body (in 59 cases the entire skeleton was X-rayed) and in measuring height and weight. For each child Elgenmark counted how many ossification centres, out of 68 possible, were present in one half of the skeleton. For each ossification centre he stated the earliest times of appearance and the time at which the ossification centre appeared in 25 % in 50 % and in 100 % of the cases.

In addition he set up for each age, tables showing how many ossification centres were present, expressed by the mean M ± 1, 2, 2 ½ and 3 standard deviations. The number of ossification centres too was then related to height. Elgenmark found that ossification centres appeared earlier in girls than in boys. Up to the age of 8 months the difference averaged 2 months and thereafter increased.

Comparison of the times of appearance of symmetrical ossification centres in 59 children revealed but slight differences. In boys there was no difference between the number of cases in which the right and left half of the skeleton was first mature. In girls there were 9 cases of earlier development of an ossification centre on the left, in 3 cases on the right. This indicates that it is immaterial whether the right or the left side is X-rayed when assessing a person's skeletal age. Torgersen (1951) X-rayed both hands of 404 children under 9 years of age. He found that in 60 cases the right side was slightly advanced in development, in 95 cases the left side was more advanced, while in the remainder there was no demonstrable difference. He concluded that the difference was too small to constitute a source of error in estimating skeletal age. Similarly Dreizen et al. (1957 a) found the difference in skeletal age of the two hands of 450 children to exceed 3 months in only 13%. The greatest difference was 6 months, found in only 1.5 %. This has been confirmed by Greulich & Pyle (1959).

Elgenmark also found a highly positive correlation between age and the number of ossification centres as well as between height and the number of ossification centres and between body weight and the number of ossification centres. By means of the tables it ought to be possible to decide whether the skeletal development of a child is normal if the child is of the same race and is living under the same circumstances as the children of the experimental series.

Elgenmark pointed out that the results should be considered with some reservation because the material was fairly small and because the children's

social status in relation to the optimum was not known.

Hoerr, Pyle & Francis found the ossification centres in Elgenmark's material to appear later than in their own material of well-circumstanced children from the Brush Foundation study. Moreover, the variation in the time of their appearance proved to be greater in the former.

Åkerlund in 1918, published an atlas on skeletal maturation based upon a series of 56 healthy children aged 8–14 years in Stockholm schools. These children were from low social strata. X-rays *of the hand, foot, and elbow for* boys and girls respectively are grouped by age and within each one year group by skeletal maturity. Åkerlund observed individual differences in the sequence of maturation of the various bones. He believed that the hand and wrist were not sufficiently representative of skeletal maturation.

Suitability of Various Regions for Assessing Skeletal Maturity

Todd studying skeletal maturation in the 6 areas hand, elbow shoulder foot, knee, and hip in children from the Brush Foundation study arrived at the result that in healthy children raised under optimum conditions, the skeleton in all 6 areas has reached the same degree of maturity.

When the same investigation was applied to X-rays from school studies, the lowest standard deviations were found in assessment of skeletal maturation of the hand. Therefore, the hand was that part of the skeleton which gave the most satisfactory results, poorer results being found for the foot, knee, elbow shoulder and hip in the named order. According to the findings of Garn & Rohmann (1960 b) assessment of skeletal maturation in the hand and foot does not afford more accuracy than assessment of the hand alone. These results are in keeping with the presumption that the hand and wrist must afford a representative picture of the entire skeletal maturation, as this area contains so many ossification centres. Since, furthermore, the hand is easy to X-ray and since it may be X-rayed without irradiation of other parts of the body, it is justified that skeletal maturation is most frequently studied in the hand.

Garn, Silverman & Rohman (1964) are working on a *system for* assessing skeletal age which takes into account that certain bones are of greater importance than others in skeletal age assessment. This was pointed out by Todd who, however, did not submit any documentation.

In order to find those ossification centres which are of most importance in a correct assessment of skeletal maturity, Garn et al., in a longitudinal study determined the time correlation between the appearance of 52 ossification centres in the hand and foot. They found 10 ossification centres in the hand and 9 in the foot to be of greater importance than the remainder. The 10 centres in the hand were among the epiphyses of the metacarpal and phalangeal bones of the 2nd–5th fingers, all of which were of greater importance in determining skeletal age than were the ossification centres in the foot.

He wanted to elucidate the time of appearance of the various ossification centres in Swedish children His material comprised 429 boys and 423 girls from Stockholm and environs, selected among children who had been examined or treated at the paediatric hospital Samariten in Stockholm All the children were healthy and in good nutritional state. A small proportion were examined several times. The study was planned as a cross-sectional survey The children were divided into 1-month groups up to 1 year of age and thereafter into 3-month groups.

The investigation consisted in X raying the left half of the body (in 59 cases the entire skeleton was X-rayed) and in measuring height and weight. For each child Elgenmark counted how many ossification centres, out of 68 possible, were present in one half of the skeleton. For each ossification centre he stated the earliest times of appearance and the time at which the ossification centre appeared in 25 %, in 50 % and in 100 % of the cases.

In addition, he set up for each age, tables showing how many ossification centres were present, expressed by the mean M ± 1 2, 2 ¹/₂ and 3 standard deviations. The number of ossification centres too was then related to height. Elgenmark found that ossification centres appeared earlier in girls than in boys. Up to the age of 8 months the difference averaged 2 months and thereafter increased.

Comparison of the times of appearance of symmetrical ossification centres in 59 children revealed but slight differences. In boys there was no difference between the number of cases in which the right and left half of the skeleton was first mature. In girls there were 9 cases of earlier development of an ossification centre on the left, in 3 cases on the right. This indicates that it is immaterial whether the right or the left side is X rayed when assessing a person's skeletal age. Torgersen (1951) X rayed both hands of 404 children under 8 years of age. He found that in 60 cases the right side was slightly advanced in development, in 95 cases the left side was more advanced, while in the remainder there was no demonstrable difference. He concluded that the difference was too small to constitute a source of error in estimating skeletal age. Similarly Dreizen et al (1957 a) found the difference in skeletal age of the two hands of 450 children to exceed 3 months in only 13% The greatest difference was 6 months, found in only 1.5 % This has been confirmed by Greulich & Pyle (1959)

Elgenmark also found a highly positive correlation between age and the number of ossification centres as well as between height and the number of ossification centres and between body weight and the number of ossification centres. By means of the tables it ought to be possible to decide whether the skeletal development of a child is normal if the child is of the same race and is living under the same circumstances as the children of the experimental series.

Elgenmark pointed out that the results should be considered with some reservation because the material was fairly small and because the children's

social status in relation to the optimum was not known.

Hoerr Pyle & Francis found the ossification centres in Elgenmark's material to appear later than in their own material of well-circumstanced children from the Brush Foundation study. Moreover the variation in the time of their appearance proved to be greater in the former.

Akerlund in 1918, published an atlas on skeletal maturation based upon a series of 56 healthy children aged 8–14 years in Stockholm schools. These children were from low social strata. X-rays of the hand, foot, and elbow for boys and girls respectively are grouped by age and within each one year group by skeletal maturity. Akerlund observed individual differences in the sequence of maturation of the various bones. He believed that the hand and wrist were not sufficiently representative of skeletal maturation.

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The carpal ossification centres were found to be of little importance in estimating skeletal age.

It is planned to include also ossification centres in the elbow, shoulder, knee, and hip in the study and to calculate the correlation between the closure of the various epiphyses in order to be able to select those centres which are of most importance in assessing skeletal age.

In the future it might be possible to concentrate on a few but important ossification centres and even obtain estimations more accurate than at present.

Systems for Assessing Stage of Sexual Maturation

Various systems for assessing stages of pubic hair and breast maturation will be reviewed below. The development is continuous, and the selected stages are defined arbitrarily. The various ways in which pubic hair maturation is described in stages are fairly consistent. The same applies to the ways of describing breast maturation. However the mere fact that different methods of assessment exist indicates that it is difficult to choose satisfactory maturational stages. If too many stages are used the classification may become inaccurate. If few stages are used, so that they may be clearly defined and easy to employ the classification may become so rough as to be of no practical interest.

It is much easier to describe the maturation when it is possible to use, instead of stages, direct measurements of the organs, e.g. of the penis and testes, or when it is possible to record the accurate time of an event, such as the menarche.

Boys

Greulich et al. (1942) have described the sexual maturation of boys by 5 stages (*maturity groups*).

1. Testes, penis, and scrotum as in early childhood. Vellus in the pubic region, no axillary hair.
2. Testes and penis a little larger. Longer slightly pigmented pubic hair at the base of the penis.
3. Testes and penis have increased in size. Slightly pigmented, straight somewhat coarser pubic hair. Axillary hair. Slightly pigmented hair on the upper lip.
4. Testes and penis somewhat larger. Dense, pigmented curled pubic hair in an area smaller than in an adult. Further growth of axillary hair and moustache.
5. Testes and penis as in an adult. Pubic hair of adult type, in some cases with extension along the linea alba. Axillary hair of adult type. Moustache as well as beard.

These maturity groups were selected after the study of photographs taken in longitudinal surveys.

Stolz & Stolz (1951), Reynolds & Wines (1951), Nicholson & Hanley (1953), Falkner (1962) and Tanner also use photographs in assessing the stage of sexual maturation in longitudinal studies on growth and development. This method does not give exact measures of the testes and penis as is also apparent from the classification. Only a few workers have used direct measurement of these organs (Reich 1924

From Hansen & With 1951 and Quaade 1955)

In the maturity groups of Greulich et al (1942) there is no distinct difference in the description of the pubic hair in stages 2 and 3 Quaade (1955) therefore, reduced the description of the *pubic hair maturation* to 4 stages

1 The infantile stage, i.e. vellus.
2 Scattered, straight, slightly pigmented pubic hair
3 Denser curled pigmented pubic hair in the area at the base of the penis.
4 Pubic hair spreading over the entire pubic triangle, in some cases also to the thighs and along the linea alba.

Reynolds & Wines (1951) describe the development of pubic hair in 5 stages

1 The infantile stage, vellus.
2 Scattered straight, pigmented pubic hair
3 Curled pigmented pubic hair
4 Fairly dense, curled pigmented hair but not of the extent seen in adults.
5 Pubic hair of adult type.

Falkner describes 6 stages, dividing Reynolds & Wines (1951) 5th stage into two, according to the extent of pubic hair

Tanner's classification is identical with Reynolds & Wines (1951)

Hansman & Maresh (1961) describe only the time of appearance of the pubic hair In the present study the author used Greulich et al's (1942) modified method for assessing pubic hair partly because it was used by Quaade (1955) in a Danish material which makes the results found in two Danish studies comparable, and partly because the stages are well-defined and fairly easy to employ

Girls

Breast maturation was described by Stratz (1904) by 4 stages

1 The infantile stage. Areola flat, nipple slightly prominent. No glandular tissue.
2 Prominence of areola and nipple and incipient development of glandular tissue.
3 Increased quantity of glandular and fatty tissue. Areola and nipple prominent, forming a separate mound above the general contour of the breast
4 Breast fully developed Areola on a level with the skin. Nipple more or less prominent.

Greulich et al (1938) refer to this description

Reynolds & Wines (1948) describe breast development in 5 stages

1 Infantile stage, elevation of the nipple.
2 Elevation of the nipple, areola, and breast.
3 Further growth and elevation of the breast and areola with no distinct separation of their contours.
4 Areola and nipple form a separate mound above the level of the breast
5 No separation of the contours of areola and breast, prominence of nipple.

Comparison of the two classifications shows that stages 2 and 3 of Reynolds

& Wines (1948) system correspond largely to stage 2 of Stratz.

Nicholson & Hanley used the classification of Stratz. Falkner described the breast development in 4 stages, but his stages are not as differentiated as Stratz' Tanner refers to Reynolds & Wines (1948) classification.

The present author used Stratz classification, partly because his stages are more clearly defined than Reynolds' & Wines' (1948) and accordingly easier to use, and partly because Stratz' classification was used by Quaade (1955) in a Danish material. This makes the results from the two Danish studies comparable.

The developmental pattern of pubic hair is the same in girls and boys, and the classifications given above for describing the maturation of pubic hair in boys apply also to girls.

The present author used Greulich et al.s (1942) modified method for the reasons stated in the section on boys.

1. The infantile stage, vellus.
2. Scattered, straight slightly pigmented pubic hair
3. Denser curled, pigmented pubic hair medially on the labia.
4. Pubic hair covering the entire pubic triangle, limited by a horizontal line superiorly

Extension to the linea alba occurs in 10 % of women and in 80 % of men (Thomas & Ferriman 1957)

From Hansen & With 1951 and Quaade 1955)

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Comparison of the two classifications shows that stages 2 and 3 of Reynolds

all the children, 12 were excluded because of diseases such as diabetes mellitus, chronic pyelonephritis, bronchial asthma, history of poliomyelitis or tuberculosis, as the object was to assess the stage of maturation in children who were clinically healthy (Table 3).

After reading of all the X rays films, yet another child had to be excluded because of multiple exostoses.

Three were excluded because they were not yet 7 years of age. This leaves 1009 children whose age distribution is shown in Table 4.

Table 4
Distribution by sex and age.

Age	Boys	Girls
7– 8 years	48	48
8– 9 –	43	40
9–10 –	57	56
10–11 –	48	49
11 12 –	48	68
12 13 –	39	46
13–14 –	32	62
14–15 –	56	[illegible]
15–16 –	[illegible]	51
16–17 –	27	50
17 18 –	15	21
18–18½ –	11	8
Total	477	532

Chapter 3

Material

The study comprised a total of 1025 children, 959 in the age range 7–17 years from a council school (Nyboder skole) and 66 aged 17–18 years from the neighbouring grammar schools Niels Steensen Østre Borgerdyd and Sortedam, all in Copenhagen

The children from Nyboder were chosen because they were believed to represent rather different socio-economic strata of the Copenhagen population This proved to be so In respect to parents occupation as well as income all groups are represented The distribution in social groups in relation to this distribution for the whole of Copenhagen is apparent from the chapter on skeletal maturation in relation to social circumstances.

The grammar-school pupils were included in order to elucidate also the last stages in the maturation of the hand skeleton.

After perusal of the health cards for

Table 3
The original material less excluded children.

From Nyboder	959 pup[illegible]	
From grammar schools	66 –	
Total	1025 pupils	10?5 pupils
Bronchial asthma	3 pupils	
Diabetes mellitus	5 –	
Chronic otitis media (paracentesis 14 times)	1 –	
History of poliomyelitis	2 –	
Chronic pyelonephritis	–	
History of tuberculosis	1 –	
Multiple exostoses	1 –	
	13 pupils	
Younger than 7 years	3 –	
Total excluded	16 pupils	16 pupil
Material studied		1009 pupils

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13–14 –	52	[illegible]
14–15 –	56	55
15–16 –	33	51
16–17 –	27	30
17–18 –	15	21
18–18½ –	11	6
Total	477	532

Chapter 4

Method

The *examination of the boys* consisted in

1. X ray of the right hand
2. Measurement of standing height.
3. Measurement of size of testes.
4. Measurement of length of penis.
5. Assessment of pubic hair mous-tache, and voice

The *examination of the girls* consisted in

1. X-ray of the right hand.
2. Measurement of standing height
3. History taking concerning time of menarche
4. Assessment of breast development.
5. Assessment of pubic hair

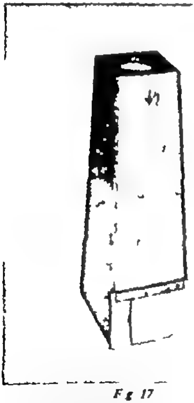

Fig 17

The box used in X-raying the hand and wrist. The box is lined with lead. The X-ray tube was placed in the circular hol in the top of the box and the X-ray film on its floor

The *examination by X ray* was done in the Dental Clinic of the Nyboder School using a dental tube.

For this purpose a wooden box was designed Its floor sides, and ceiling were lined with lead (Fig 17)

The floor measured 19×25 cm to accommodate an 18×24 cm film (the *film size most often used in X raying* hands) The top was provided with a circular hole *to* admit the X ray tube *during the exposure In this way* the focus-film distance was constant 7? cm

The figure shows, at the bottom of the box on one side an opening to admit the film and the hand to be X-rayed The right hand is placed with extended fingers and the volar side of the hand and wrist on the middle of the film (Fig 18)

The use of this box involves two advantages

1. Radiation is restricted to the child's right hand.
2. The focus-film distance is constant. The exposure factors were 60 kV 16 mA, and 0.8–1 2 sec. Only Sino films were used. The films were heavily exposed and read in strong light.

5 boys had to be X-rayed again, because the first films had not included the entire distal epiphysis of the radius.

Height was measured at full stretch, applying gentle traction under the mastoid processes and telling the child to stretch up as much as possible (technique of Tanner) The measurements were made by the school nurse after instruction and subsequent checking

Height was recorded as the nearest whole cm as done by Dossing (1950) One measurement was made on each pupil.

Fig 18.

Positioning of boy for an X-ray of the hand and wrist. At the bottom of the box, on one side, an opening to admit the hand. The fingers are extended and the volar side of the hand and wrist rests on the middle of the film

Boys

Testes. By a slide caliper 3 polar measurements were obtained on both sides. The tables state the mean measurement in mm. There is a linear correlation between the polar measurement and the volume of the testis (Quaade 1955)

Penis The length of the penis was measured by supporting the slide caliper against the symphysis at the base of the penis and placing the penis along the scale of the slide caliper The measurement was read in mm at the tip of the penis regardless of the appearance of the prepuce. The mean of 3 measurements was recorded.

Pubic hair was estimated by a method described by Greulich et al. (1942) and used by Quaade (1955) in a Danish material. The development of the pubic hair was divided into 4 stages

1. Vellus, the infantile stage.
2. Scattered pigmented, straight hair
3. Curled pigmented hair at the base of the penis.
4. Spread of curled pigmented hair to a larger area, in some cases along the linea alba and the medial sides of the thighs.

It was noted whether a *moustache*

Chapter 4

Method

The examination of the boys consisted in

1 X ray of the right hand
2 Measurement of standing height.
3 Measurement of size of testes.
4 Measurement of length of penis.
5 Assessment of pubic hair, moustache, and voice.

The examination of the girls consisted in

1 X ray of the right hand.
2 Measurement of standing height.
3 History-taking concerning time of menarche.
4 Assessment of breast development.
5 Assessment of pubic hair

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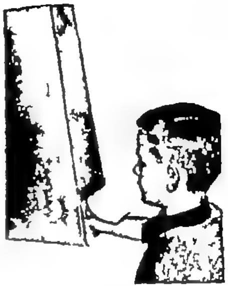

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It was noted whether a *moustache*

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3. Measurement of size of testes.
4. Measurement of length of penis.
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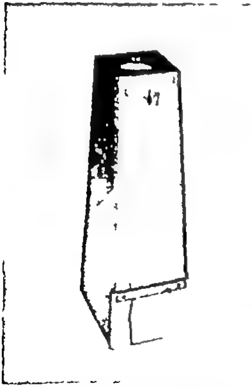
The examination of the girls consisted in

1. X ray of the right hand.
2. Measurement of standing height.
3. History taking concerning time of menarche.
4. Assessment of breast development
5. Assessment of pubic hair



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The use of this box involves two advantages

Procedure of Determining Skeletal Age

The skeletal age was assessed both by Greulich & Pyle's atlas and by the system of Tanner & Whitehouse. The assessment was done without the author knowing the chronological age of the child whose X-ray film was being read. The skeletal age was stated, as done by Greulich & Pyle, in the nearest whole or half year. The accuracy of this procedure will be discussed in Chapter 6.

By reading about 300 films of the hand skeleton of children of all ages, which had previously been read by an experienced radiologist using the Greulich & Pyle atlas, and comparing my results with his, I had attained considerable practice in the use of Greulich & Pyle's atlas.

Preliminary Result

To gain a preliminary impression of the skeletal age in relation to chronological age in this material the difference between skeletal age and chronological age was calculated for every 10th girl and boy. Assessed by the method of Greulich & Pyle, the skeletal age was about 5 months below the chronological age. Assessed by the system of Tanner & Whitehouse, the skeletal age deviated, for boys aged 7–15 years and for girls aged [illegible]–13 years, by only a few months from the chronological age, while for the ages above this there was a striking difference between skeletal and chronological age suggesting possible faults of the method or errors in assessing the skeletal age of the almost full-grown children.

As described in discussing the method of Tanner & Whitehouse, a bone must fulfill certain maturity criteria to be assessed as having attained a certain stage of maturation. For instance, the criterion for the navicular bone to have reached its final stage is "The gaps between the navicular bone and the greater and lesser multangulars, capitate, and lunate are reduced to their adult dimensions. There is virtual contact between the navicular and the lunate throughout the whole of their adjacent borders" If there is no virtual contact between the navicular and the lunate, the navicular has reached only stage 7 If the film is, say from a girl of 13 whose stage of skeletal maturation corresponds approximately to her chronological age, a difference from stage 7 to 8 for the navicular gives a difference in skeletal age of only a few months, but if the film is

i.e. pigmented hair was present laterally on the upper lip

Lastly it was estimated whether the *voice* had broken

Girls

The girls were asked whether the *menarche* had occurred and if so when

Breast development was assessed by a classification into 4 stages as described by Stratz and used by Quaade (1955)

1 The infantile stage in which the areola is flat, the nipple slightly prominent no glandular tissue.
2 Prominence of the areola and nipple, incipient development of glandular tissue.
3 Increased amount of glandular and fatty tissue. Areola and nipple still prominent, forming a separate mound above the level of the breast.
4 Breast fully developed. Areola on a level with the skin, nipple more or less prominent

Pubic hair was estimated by criteria corresponding to those used for the boys

1 Vellus, the infantile stage.
2. Scattered pigmented straight hair
3 Pigmented curled hair on the labia and mons pubis around the midline.
4 Fully developed pubic hair of a feminine distribution limited by a horizontal line superiorly

Chapter 5

Procedure of Determining Skeletal Age

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Preliminary Result

To gain a preliminary impression of the skeletal age in relation to chronological age in this material, the difference between skeletal age and chronological age was calculated for every 10th girl and boy. Assessed by the method of Greulich & Pyle, the skeletal age was about 6 months below the chronological age. Assessed by the system of Tanner & Whitehouse, the skeletal age deviated for boys aged 7–15 years and for girls aged 7–13 years, by only a few months from the chronological age, while for the ages above this there was a striking difference between skeletal and chronological age, suggesting possible faults of the method or errors in assessing the skeletal age of the almost full-grown children.

As described in discussing the method of Tanner & Whitehouse, a bone must fulfill certain maturity criteria to be assessed as having attained a certain stage of maturation. For instance, the criterion for the navicular bone to have reached its final stage is "The gaps between the navicular bone and the greater and lesser multangulars, capitate, and lunate are reduced to their adult dimensions. There is virtual contact between the navicular and the lunate throughout the whole of their adjacent borders." If there is no virtual contact between the navicular and the lunate, the navicular has reached only stage 7. If the film is, say from a girl of 13 whose stage of skeletal maturation corresponds approximately to her chronological age, a difference from stage 7 to 8 for the navicular gives a difference in skeletal age of only a few months, but if the film is of an almost full-grown girl, the same

difference in the assessment of the navicular will give a difference of more than 2 years in the assessment of skeletal age. This is due to the fact that the rating scale for the carpal bones increases abruptly to the last stage from the last but one and that the rating scale for the entire hand increases very slowly in the older age groups.

At times, it may be difficult to decide whether the bone is to be rated as stage 7 or 8 when dealing with the greater multangular the lesser multangular the lunate, the hamate, and the triquetral If the triquetral is to be assessed as having reached stage 8 the following criterion has to be fulfilled "The distal portion has now broadened so that it is nearly or quite as wide as the proximal portion" or the bone has now its adult appearance, and there is frequently overlapping between the edges of the triquetral and the hamate In fact it is frequently impossible to decide with certainty whether the bone has reached stage 7 or 8 Normally the round bones are completing their maturation around puberty before the fusion of epiphyses with diaphyses occurs in the metacarpal and phalangeal bones.

Although I had tried to follow the instructions as accurately as possible, I got strikingly low skeletal ages for the older age groups.

Visiting the Institute of Child Health Department of Growth and Development" University of London I had the opportunity of discussing my results with J M Tanner and R. H. Whitehouse They pointed out that in addition to rating each bone separately it is important in the assessment, to view the hand as a whole, and when the process of epiphyseal closure in the fingers was under way it could be deduced that the development of the carpal bones had been completed, and these bones could therefore be rated as in an adult.

To ascertain whether my use of Tanner & Whitehouse's method was in other respects justified I estimated in blind experiments 119 films of children of all ages which had previously been assessed by Tanner and Whitehouse. The two assessments proved identical apart from the fact that consistently I estimated the skeletal age as being a month or two higher

After having received the named instruction in assessing the carpal bones, I repeated my assessment of the films of boys who were over 13 years of age and girls who were over 11 Thus, I felt that I had repeated the assessment of all films in which the carpal bones had reached stage 7 or 8

The first and second assessments by the Tanner & Whitehouse system will be called Tanner & Whitehouse I and II

Chapter 8

Result and Accuracy of Skeletal Age Assessment

Tables 5 and 6 give, for boys and girls respectively means (M) and standard deviations (SD) for the difference between the chronological ages and skeletal ages assessed by the Greulich & Pyle and the Tanner & Whitehouse methods. Two series are listed, I and II for skeletal ages assessed by the system of Tanner & Whitehouse. These skeletal ages are identical for the younger age groups, but from the age of 13 for the boys and 11 for the girls a new assessment was done, as already mentioned, i.e. series II. Furthermore, the tables give the difference in skeletal age when assessed according to Greulich & Pyle and according to Tanner & Whitehouse.

Skeletal age (SA) assessed by the method of Greulich & Pyle is seen to be on the whole lower than chronological age (CA) indicating that the children of the American material were mature earlier than those of the Danish material. This is quite likely according to what is apparent from the chapter on maturation in relation to social circumstances, as the children of the American study were from homes far above the average educational and economic level. The difference averages 3.9 and 5.2 months for boys and girls respectively

Assessment of the films by the method of Tanner & Whitehouse, i.e. Tanner & Whitehouse II which is supposed to be the more correct assessment, showed that skeletal ages for boys as well as for girls in this country are on an average 2.3 months above the chronological ages. As far as the oldest girls are concerned, however the skeletal ages, assessed by the method of Tanner & Whitehouse, were on the average lower than the chronological ages. The explanation is presumably that the upper limit of skeletal maturity which is fixed in Tanner & Whitehouse's system arbitrarily at 17 years, is low for the girls of the present material.

The difference between skeletal age and chronological age varied from age to age. The same finding has been made in other materials in which the skeletal age in different groups of children has been determined according to the atlas of Greulich & Pyle. This variation in the difference between skeletal age and chronological age may be due to a certain heterogeneity in the assessment, since the assessment is earlier at some ages than at others. Apart from this, it may be due to a difference between the materials upon which the systems for skeletal age estimation are based and the present material. In as-

difference in the assessment of the navicular will give a difference of more than 2 years in the assessment of skeletal age. This is due to the fact that the rating scale for the carpal bones increases abruptly to the last stage from the last but one and that the rating scale for the entire hand increases very slowly in the older age groups.

At times, it may be difficult to decide whether the bone is to be rated as stage 7 or 8 when dealing with the greater multangular the lesser multangular the lunate, the hamate, and the triquetral. If the triquetral is to be assessed as having reached stage 8 the following criterion has to be fulfilled 'The distal portion has now broadened, so that it is nearly or quite as wide as the proximal portion or the bone has now its adult appearance, and there is frequently overlapping between the edges of the triquetral and the hamate In fact it is frequently impossible to decide with certainty whether the bone has reached stage 7 or 8 Normally the round bones are completing their maturation around puberty before the fusion of epiphyses with diaphyses occurs in the metacarpal and phalangeal bones.

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sessing the films in Greulich & Pyle's atlas by the method of Tanner & Whitehouse for the age from 7 years and upwards, I found, for boys as well as for girls, an average difference of 7.1 months. The difference varied from age to age. In the older ages it was slight and in the younger ages greater. This variation in the difference between skeletal age and chronological age makes the total SD given in the extreme right hand column of Tables 5 and 6 somewhat greater than the average SD for the individual age groups.

Standard Deviation of the Skeletal Age Assessment

The total standard deviation includes the biological variation as well as the error of measurement of the skeletal age assessment. As the biological variation is the same in the various methods of assessment, a difference in total standard deviations, when using the two different methods, must indicate a difference in the error of measurement. However the differences in the standard deviations when the films were assessed by the method of Tanner & Whitehouse and by that of Greulich & Pyle are so slight that one method cannot be said to be more accurate than the other. The total SD for boys by Greulich & Pyle's method is 12.5 months, by Tanner & Whitehouse's method I 13.0 and by Tanner & Whitehouse II 13.3 months. The total SD for the girls by Greulich & Pyle is 11.9 months, by Tanner & Whitehouse I 13.1 months, and by Tanner & Whitehouse II 11.5 months.

By direct comparison of the assessed skeletal ages by the methods of Greulich & Pyle and of Tanner & Whitehouse, it is possible to estimate the error of measurement, presupposing that the errors of measurement are equally great and also independent, i.e. that the two methods do not employ the same criteria. This presupposition is only partially fulfilled.

The difference between skeletal ages measured by Tanner & Whitehouse's and by Greulich & Pyle's methods averages 8.4 months for the boys and 7.7 months for the girls. The total SD is 8.9 months for boys as well as for girls. Accordingly the error of measurement of a single reading has a SD of $\frac{8.9}{\sqrt{2}}$ which gives 6.3 months.

For a fixed chronological age, the variance of skeletal age must be equal to the sum of the biological variance and the variance of the error of measurement. The SD of the error of measurement being 6.3 months, the variance is the square of this value, or 39 months, and the variance in skeletal age will then, when using the Greulich and Pyle method average 12.2^2 or 149 months for boys and girls. Accordingly the biological variance will be 149 − 39 = 110 months. Extraction of the square root of this value gives the biological SD 10.5 months.

Although these estimates carry a fairly marked uncertainty they probably represent the proportionate significance of the two factors. By the method of Greulich & Pyle the skeletal age is recorded, as mentioned above, in the nearest whole or half years. It may be calculated that the total variance

les 5 and 6 Differences between skeletal age and chronological age in assessing the X ray films by Greulich & Pyle's atlas and by Tanner & Whitehouse
m. Differences in skeletal age when the films were assessed by the methods of Greulich & Pyle and of Tanner & Whitehouse. Tanner & Whitehouse I an
II indicate the results of 2 different assessments. The results are tated as mean differences (M) and standard deviations (SD) both in months.

Table 5
Boys

Chronological age in hole years	7	8	9	10	11	12	13	14	15	16	17	18	Mean	Total
of boys	48	43	57	48	48	39	52	56	33	27	15	11		
ulich & Pyle M	−7.5	−10.3	−5.9	−5.2	−5.4	−3.3	−5.1	−6.4	−6.6	−7.9	+1.3	+0.3	−5.9	
ulich & Pyle SD	11.4	12.4	12.4	16.2	13.0	11.2	9.8	11.7	13.5	13.1	11.8	9.1	12.4	12.5
ner & Whitehouse I M	−2.2	+2.5	+0.9	−0.4	−1.6	+0.3	+3.2	+1.6	−2.0	−8.5	+5.7		0.0	
ner & Whitehouse I SD	14.4	12.2	11.6	16.4	14.2	15.2	12.3	10.9	9.5	7.8	10.2		12.8	13.0
ner & Whitehouse II M							+6.8	+5.2	+7.3	+4.6	+8.8		+2.3	
ner & Whitehouse II SD							12.8	10.7	11.6	10.6	6.3		13.0	13.3
nner & Whitehouse II − Greulich Pyl M	+5.3	+12.8	+6.8	+4.8	+3.8	+3.6	+11.9	+11.6	+13.9	+12.5	+7.5		+8.4	
nner & Whitehouse II − Greulich Pyle SD	10.4	7.2	7.8	8.1	10.7	7.5	6.6	6.5	7.3	5.9	9.8		8.1	8.9

Table 6
Girls

Chronological age in hole years	7	8	9	10	11	12	13	14	15	16	17	18	Mean	Total
. of girls	48	40	56	49	68	46	62	55	51	30	21	6		
reulich & Pyle M	−4.4	−7.1	−11.7	−5.7	−7.6	−4.6	−2.3	−3.1	−3.9	+2.2	−3.1		−5.2	
reulich & Pyle SD	12.3	9.1	10.5	10.8	12.5	10.6	12.8	13.3	13.6	9.9	8.9		11.5	11.9
anner & Whitehouse I M	+1.0	+4.1	−1.4	+2.7	+0.1	+1.9	−2.2	−5.1	−17.4	−22.5			−3.2	
anner & Whitehouse I SD	12.2	11.0	10.0	12.6	11.6	7.2	8.3	10.4	9.6	15.9			10.8	13.1
anner & Whitehouse II M					+0.7	+0.9	+7.5	+4.5	−2.2	−4.1			+2.3	
anner & Whitehouse II SD					12.7	10.1	9.8	10.6	9.3	8.3			10.8	11.5
anner & Whitehouse II − Greulich Pyle M	+5.4	+11.2	+10.3	+8.4	+8.3	+13.6	+9.8	+7.1	+1.7	−6.3			+7.7	
anner & Whitehouse II − Greulich Pyle SD	9.0	7.0	6.7	7.2	9.1	6.6	8.1	7.3	8.7	6.0			7.6	8.9

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Mainland (1954) has investigated the variable error by assessing different series of films by the Greulich & Pyle atlas. He found the SD of the differ ence between duplicate assessments to be less than 3 months in some experi ments and slightly more than 4 months in others. Greulich & Pyle (1959) state that the assessment of X ray films car ries subjective errors and that the cer tainty of the assessment is expressed by the ability of the examiner to reproduce his readings. Referring to Mainland s variable error expressed in standard deviations of 3–4 months they state that this error is possibly rather high as the examiner was inexperienced in reading films. Greulich & Pyle do not report any investigations of their own into errors of measurement

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The Systematic Error

Acheson (1963) made 8 examiners, 6 of whom were experienced and 2 in experienced assess the films of the hand skeletons of 50 boys and 50 girls ac cording to the Greulich & Pyle atlas and calculated the average skeletal age for all 100 films assessed by each ex aminer This showed a 4 month dif ference in skeletal age in the results of those examiners who had assessed the highest and lowest skeletal age. The in experienced examiners obtained values between the extreme values. Mainland (1953) found a systematic error of 4–5 months.

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Todd found that examiners of wide ly different experience in reading films do so with an accuracy of 6 months or less.

Discussion of the Size of the Standard Deviation

Since the standard deviations in assessing the present material by the methods of Greulich & Pyle and of Tanner & Whitehouse averaged 12.2 and 12.4 months respectively and thus were of the same magnitude as found by previous authors, the error of measurement in the present assessment of skeletal age is of a magnitude similar to those of others. As already mentioned, Greulich & Pyle found that the standard deviation in assessing the skeletal age of children aged 7 years and more averaged 10.6 months, i.e. somewhat lower than in the present study. This may be due to the biological variation in the healthy and well-to-do Brush Foundation material being less than in the present material. Assessment of children from Boston many of whom were of a socially poorer stratum than the Brush Foundation children, revealed an average SD of 11.6 months (Greulich & Pyle 1959). As mentioned above, the standard deviations in the material assessed by Tanner & Whitehouse by their own method was 12–12.5 months.

Preferred Method for Assessment of Skeletal Age

In analysing the relationship between skeletal maturation and other maturational criteria, the author used the results obtained by assessing skeletal age by Greulich & Pyle's atlas, partly because this method can be learnt far more quickly than Tanner & Whitehouse's and partly because it proved to be equally accurate.

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Table 7

Height tables from Sweden, Norway and Denmark as well as from the Brush Foundation study

Boys

Age	Broman, Dahlberg & Lichtenstein, Sweden 1938–39 Height cm	SD cm	[illegible], Bergen [illegible] Height cm	SD cm	Oslo, School health service [illegible] Height cm	Dearing, Denmark 1930–1942 Height cm	SD cm	Present study 1964 Height cm	SD cm	The Brush Foundation study US 1931–1942 Height cm	SD cm
7 years (6 ½–7½)	125.0	3.2	124.9	5.0	1?8.1	121.8	5.6	127	4.8	125.8	4.7
								128			
8	128.5	5.5	128.5	5.5	129.4	127.3	5.7	130	4.8	129.8	4.8
								134			
9 –	133.5	5.8	133.7	5.6	134.5	132.4	5.9	138	4.9	135.3	5.0
								140			
10	138.5	6.0	138.5	5.7	139.5	137.2	6.1	142	6.7	141.0	5.5
								144			
11	143.3	6.4	143.0	6.2	144.6	142.0	6.4	146	6.7	145.9	6.0
								148			
12	148.0	7.2	148.6	6.7	149.8	146.9	6.9	152	7.5	151.4	6.8
								155			
13	153.6	7.9	154.4	7.8	156.1	152.6	8.1	161	7.1	157.5	7.8
								164			
14 –	160.5	8.5	161.5	8.6	162.8	159.5	9.0	165	8.4	164.6	8.4
								167			
15 –	166.6	8.4	166.9	8.1	170.1	167.0	8.2	169	8.7	171.1	7.3
								172			
16 –	172.5	7.9	171.6	7.2	175.3	172.1	7.3	174	7.3	175.2	6.2
								175			
17 –	175.7	7.0			178.1	175.2	6.9	179	6.5	178.6	5.7
								181			
18 –	177.5	6.5			179.3	176.1	6.7	181	6.0		
19 –	178.0	6.2									
20 –	178.2	6.0									

Dearing's heights are shifted half a year in relation to the others, because the average heights in his study were calculated for whole completed years. The heights in the present material were calculated for whole completed years as well as for the nearest year.

Chapter 7

Height

Introduction

In Chapters 7–13 an attempt will be made to evaluate to what extent skeletal age is applicable as a standard of biological maturation by comparing it with other criteria of maturation, such as height, menarche, maturation of breasts and of pubic hair etc.

Evaluation of skeletal age as a standard of biological maturation was done by comparing the relation of the named criteria to skeletal age with the relation of the same criterion to chronological age. In practice, this was done by grouping the material by skeletal age as well as by chronological age and by investigating for each subgroup the change in the maturational degree of the various criteria when the skeletal age and chronological age respectively are increased by one year

The curves illustrating the relation of the various maturational criteria to chronological age represent maturation in so far as it may be assumed that the present material is a representative section of children in the Danish population The curves present a snapshot of the maturation as the study was cross-sectional.

Previous Studies of Height

Tables 7 and 8 give, for boys and girls respectively a number of height tables from Sweden, Norway and Denmark as well as the height tables from the Brush Foundation study

Broman, Dahlberg & Lichtenstein's tables, which comprise children and adolescents from 1 to 20 years of age, were worked out on the basis of cross-sectional studies of 8441 children from maternity departments, day nurseries, nursery and other schools in Stockholm Malmö and Östergotland from the period 1938–1939 Tables 7 and 8 give only the results for the ages after 7 years, as the youngest children of the present study were 7 Broman, Dahlberg & Lichtenstein's tables are often used in Denmark.

Sundal (1957) analysed the height of 17 795 boys and girls in Bergen, Norway His material comprised measurements of the length of all newborn infants in Bergen in 1955 height measurements from the health centre of the Bergen Children's Hospital during the period 1952–1955 and height measurements done in March 1956 on 12 684 boys and girls aged 7–16 years in the Bergen schools.

In Norway the height and weight of Oslo school children aged 7–14 years has been recorded since 1920 in March of every year Every 5th

Table 7

Height tables from Sweden Norway and Denmark as well as from the Brush Foundation study

Boy

Age	Broman, Dahlberg & Lichtenstein, Sweden 1938-1939		Sundal, Bergen 1956		Oslo, School health studies 1967	Dansing, Denmark 1923-1942		Present study 1964		The Brush Foundation study US 1931-1942	
	Height cm	SD cm	Height cm	SD cm	Height cm	Height cm	SD cm	Height cm	SD cm	Height cm	SD cm
7 years (6½–7½)	125.0	5.2	124.9	5.0	126.1	121.8	5.6	127	4.8	123.8	4.7
								128			
8 –	128.5	5.5	128.3	5.5	129.4	127.3	5.7	130	4.8	129.8	4.8
								134			
9 –	133.5	5.8	133.7	5.6	134.5	132.4	5.9	138	4.9	135.3	5.0
								140			
10	138.5	6.0	138.5	5.7	139.5	137.2	6.1	142	6.7	141.0	5.5
								144			
11	143.3	6.4	143.0	6.2	144.6	142.0	6.4	146	6.7	145.9	6.0
								148			
12	148.0	7.2	148.6	6.7	149.6	146.9	6.9	152	7.5	151.4	6.8
								155			
13 –	153.6	7.9	154.4	7.8	156.1	152.6	8.1	161	7.1	157.5	7.8
								164			
14 –	160.5	8.5	161.5	8.6	162.8	159.8	9.0	165	8.4	164.8	8.4
								167			
15 –	166.6	8.4	166.9	8.1	170.1	167.0	8.2	169	8.7	171.1	7.3
								172			
16 –	172.3	7.9	171.8	7.2	175.3	172.1	7.3	174	7.3	175.2	6.2
								175			
17 –	174.7	7.0			178.1	175.2	6.9	179	6.5	1 6.6	5.7
								181			
18 –	177.5	6.5			179.3	178.1	6.7	181	6.0		
19 –	178.0	6.2									
20 –	178.2	6.0									

Dansing heights are shifted half year in relation to the others because the average heights in his study were calculated for whole completed years. The heights in the present material were calculated for whole completed years as well as for the nearest year

Chapter 7

Height

Introduction

In Chapters 7–13 an attempt will be made to evaluate to what extent skeletal age is applicable as a standard of biological maturation by comparing it with other criteria of maturation such as height, menarche, maturation of breasts and of pubic hair etc.

Evaluation of skeletal age as a standard of biological maturation was done by comparing the relation of the named criteria to skeletal age with the relation of the same criterion to chronological age. In practice, this was done by grouping the material by skeletal age as well as by chronological age and by investigating for each subgroup the change in the maturational degree of the various criteria when the skeletal age and chronological age respectively are increased by one year

The curves illustrating the relation of the various maturational criteria to chronological age represent maturation in so far as it may be assumed that the present material is a representative section of children in the Danish population The curves present a snapshot of the maturation, as the study was cross-sectional

Previous Studies of Height

Tables 7 and 8 give for boys and girls respectively a number of height tables from Sweden Norway and Denmark as well as the height tables from the Brush Foundation study

Broman Dahlberg & Lichtenstein's tables, which comprise children and adolescents from 1 to 20 years of age, were worked out on the basis of cross-sectional studies of 8441 children from maternity departments, day nurseries, nursery and other schools in Stockholm Malmö and Östergötland from the period 1938–1939 Tables 7 and 8 give only the results for the ages after 7 years, as the youngest children of the present study were 7 Broman Dahlberg & Lichtenstein's tables are often used in Denmark.

Sundal (1957) analysed the height of 17 795 boys and girls in Bergen Norway His material comprised measurements of the length of all newborn infants in Bergen in 1955 height measurements from the health centre of the Bergen Children's Hospital during the period 1952–1955 and height measurements done in March 1956 on 12 684 boys and girls aged 7–16 years in the Bergen schools.

In Norway the height and weight of Oslo school children aged 7–14 years has been recorded since 1920 in March of every year Every 5th

year the average height for each age has been calculated (Tables 9 and 10) From 1939 moreover the height of children from grammar schools has been recorded, so that from 1960 the tables contain height measurements for children aged 7–18 years. Almost 60,000 children have been measured. Through this period height has shown an increasing trend. However analysis of the values for 1955 showed that the increase in height had been considerably reduced, so that presumably the maximum had been reached. Bakwin & McLaughlin (1964) also found the increase in height to be decelerating, boys entering Harvard from municipal schools being 3.5 cm taller than 25 years ago, while the average height for boys entering Harvard from private schools had not altered during this period. Furthermore, pupils who came to Harvard from municipal schools in the years 1958–59 were of the same average height as the boys from private schools.

Table 9.

Height of schoolboys in Oslo 1920–1960.

Year	7 years ([illegible])	8	9	10	11	12	13	14
	cm	cm	cm	cm	cm	cm	cm	cm
1920		121.8	126.1	130.9	135.0	139.2	143.3	148.2
1925		123.5	128.6	132.9	137.8	141.3	145.8	150.5
1930		125.2	130.6	135.1	139.8	142.9	147.8	153.1
1935		127.2	132.1	136.8	140.9	145.7	150.5	155.5
1940		128.3	133.3	138.5	142.4	147.1	152.9	157.6
1943		127.7	132.9	137.6	142.5	147.0	153.2	157.9
1945	123.7	127.4	132.5	137.3	142.2	147.1	152.9	157.8
1947	123.2	128.6	133.7	138.4	143.2	147.9	153.4	158.5
1950	123.7	128.9	134.5	139.0	144.0	149.0	154.5	160.7
1955	126.1	129.3	134.7	139.9	144.9	149.7	155.2	161.9
1960	126.1	129.4	134.5	139.5	144.6	149.8	156.1	162.8

Table 10

Height of schoolgirls in Oslo 1920–1960.

Year	7 years ([illegible])	8	9	10	11	12	13	14
	cm	cm	cm	cm	cm	cm	cm	cm
1920		120.6	125.3	130.0	135.1	140.4	145.6	150.6
1925		122.5	127.8	132.3	137.2	142.4	147.9	152.4
1930		124.7	129.7	134.6	139.5	144.8	150.4	154.9
1935		126.4	131.3	136.7	141.5	147.5	153.1	157.3
1940		127.4	132.6	137.7	143.2	149.1	155.0	158.6
1943		126.9	131.7	136.7	142.4	148.4	154.6	158.4
1945	123.1	126.5	131.4	136.8	141.8	147.6	154.2	158.4
1947	124.4	128.0	133.2	137.8	143.2	149.4	155.0	158.7
1950	124.9	128.1	133.3	138.9	144.6	150.7	156.2	159.8
1955	125.0	128.6	133.7	139.0	145.1	151.2	156.9	160.4
1960	125.1	128.2	133.5	138.9	144.4	150.6	157.0	161.8

Table 8

Height tables from Sweden, Norway and Denmark as well as from the Brush Foundation study

Girls.

	Bromans, Dahlberg & Lichtenstein, Sweden 1938–1939		Sundal, Bergen 1956		Oslo School health studies 1960	Densing, Denmark 1939–1942		Present study 1964		The Brush Foundation study USA 1931 1942	
Age	Height cm	SD cm	Height cm	SD cm	Height cm	Height cm	SD cm	Height cm	SD cm	Height cm	SD cm
7 years (6 ½–7½)	122.3	5.3	123.4	4.9	123.1					123.7	5.1
						121.1	5.5	126	5.1		
8 –	127.0	5.7	127.0	3.2	128.1			128		129.8	5.3
						126.4	5.7	131	5.9		
9 –	132.5	6.1	132.2	5.7	133.5			131		135.3	5.6
						131.6	5.9	134	6.2		
10 –	137.5	6.6	137.4	5.8	138.9			138		141.0	5.9
						136.9	6.3	144	6.5		
11 –	142.8	7.0	143.6	6.9	144.4			144		147.7	6.5
						142.6	7.0	146	7.2		
12 –	148.9	7.2	149.7	7.4	150.6			150		154.2	6.8
						148.6	7.3	153	7.2		
13 –	155.0	6.9	155.3	6.9	157.0			156		159.5	6.2
						154.0	7.0	158	6.2		
14 –	159.0	6.5	159.8	6.2	161.8			159		162.8	5.9
						158.5	6.2	162	5.7		
15 –	162.0	6.1	161.4	5.9	164.0			163		164.8	5.3
						161.2	5.8	164	4.3		
16 –	164.0	5.8	161.5	6.2	165.4			164		165.4	5.5
						162.3	5.5	162	6.4		
17	164.5	5.5			166.1			165		165.3	5.1
						163.6	5.3	168	6.2		
18 –	165.0	5.4			166.6			167			
						164.2	5.2	166	4.6		
19 –	166.0	5.2									
20 –	166.0	5.1									

Densing's heights are shifted half line in relation to the others, because the average heights in his study were calculated for whole completed years. The heights [illegible] the present material were [illegible]alculated for whole completed years as well as for the nearest year

from 126 to 162, corresponding to an average annual height increment of about 5 cm.

The curve representing the boys growth in height runs a somewhat steeper course in the age group 12–15 years, indicating the faster growth during these years (the adolescent growth spurt) The girls curve is more even, presumably because the girls growth spurt is not as pronounced as the boys

If the Swedish, Norwegian, and American height tables are plotted graphically the curves are very reminiscent of Figs. 19 and 20. Their course is fairly parallel, but they are shifted a few cm from each other Figs. 21 and 22 illustrate the height curves for boys and girls of the Brush Foundation study of the present material, and of Broman, Dahlberg & Lichtenstein s material.

A calculation, for each age group, of the difference in height between the Brush Foundation material and the others shows that the children of the Brush Foundation material are tallest.

In the present material the boys were an average of 2.2 cm shorter and the girls an average of 2.8 cm shorter than the children of the American series. This corresponds to about [illegible] months of "height age" the mean annual

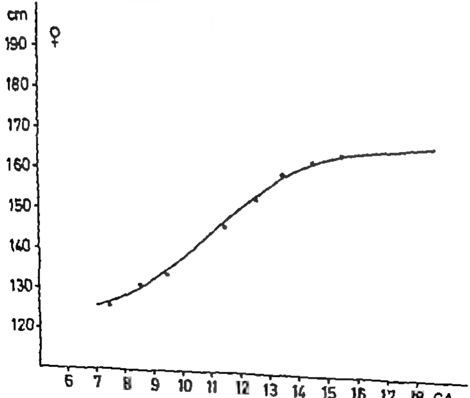

Fig 20

Height in relation to chronological age for the

The most recent analysis on the height of Danish children was performed by Døssing in 1950. From municipal primary schools and municipal grammar schools in Copenhagen he collected and analysed 17 439 height measurements from the health cards of the school health service from the 1930'ies and early forties. For each child included in the study there is a series of at least 6 measurements obtained at 1 year intervals.

Result of Height Analysis in the Present Study

Figs. 19 and 20 as well as Tables 11 and 12 present the variation in heights with chronological age for boys and girls of the present material. The curves afford an estimate of the average growth in height which will be found if a group of boys and girls born at the same time are followed by regular height measurements. As far as the boys are concerned the average height increases from 7 to 17 years of age from 127 to 179 cm i.e. by 52 cm corresponding to the average annual height increment of about 5 cm.

As far as the girls are concerned, height growth seems to decrease at the age of 14. The average height increases from 7 to 14 years of age by 36 cm,

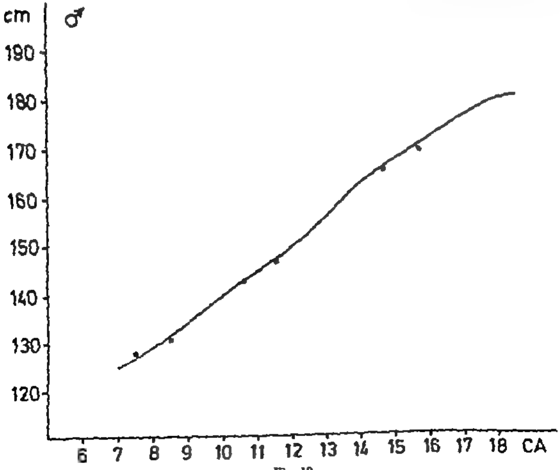

Fig. 19

Height in relation to chronological age for the boys of the present material.

from 126 to 162, corresponding to an average annual height increment of about 5 cm.

The curve representing the boys' growth in height runs a somewhat steeper course in the age group 12–15 years, indicating the faster growth during these years (the adolescent growth spurt). The girls' curve is more even, presumably because the girls' growth spurt is not as pronounced as the boys'.

If the Swedish, Norwegian, and American height tables are plotted graphically the curves are very reminiscent of Figs. 19 and 20. Their course is fairly parallel, but they are shifted a few cm from each other. Figs. 21 and 22 illustrate the height curves for boys and girls of the Brush Foundation study of the present material, and of Broman, Dahlberg & Lichtenstein's material.

A calculation, for each age group of the difference in height between the Brush Foundation material and the others shows that the children of the Brush Foundation material are tallest.

In the present material the boys were an average of 2.2 cm shorter and the girls an average of 2.8 cm shorter than the children of the American series. This corresponds to about [illegible] months of "height age" the mean annual

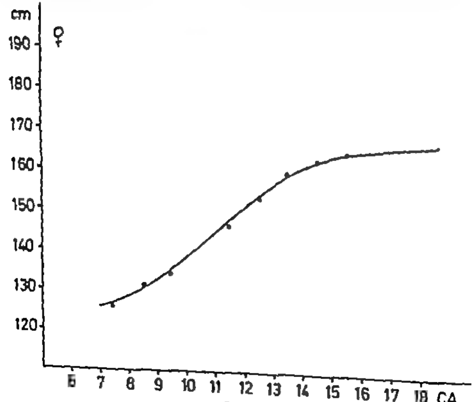

Fig. 20

Height in relation to chronological age for the girls of the present material.

Table 11

Height in relation to skeletal age and chronological age with standard deviations. SD indicates the standard deviation when the SA as well as the CA are constant.

Boys

SA (years)	Number	M cm	SD cm	CA (years)	Number	M cm	SD cm	SD* cm
5	4	123	3 3					
6	23	125	3 7					
7	41	128	4 5	7– 8	48	127	4.8	3 8
8	37	134	4 7	8– 9	43	130	4.8	4 0
9	43	136	4 6	9–10	57	138	4 9	4.5
10	41	142	5 4	10–11	48	142	6 7	5 0
11	37	147	6.7	11–12	48	146	6.7	5.8
$11^{9}/_{12}$	35	146	6.3					
$12^{6}/_{1}$	41	155	5 6	12–13	39	152	7.5	5.5
13	23	158	4.9	13–14	52	161	7 1	4.9
$13^{9}/_{12}$	22	162	5 8					
14	54	168	6.9	14–15	56	165	8.4	6.4
15	17	172	6.9	15 16	33	169	8.7	7.8
$15^{9}/_{12}$	10	174	6.5					
16	9	172	6.8	16–17	27	174	7.3	6 4
17	21	176	6 4	17–18	15	179	6.5	6.7
18	13	181	5 5	18–18 /	11	181	6 0	5 7
19	6	183	5.5					
Total	477		5 7		477		6 8	5 4

Table 12

Height in relation to skeletal age and chronological age with standard deviations. SD* indicates the standard deviation when the SA as well as the CA are constant.

Girls

SA (years)	N mber	M cm	SD cm	CA (years)	Number	M cm	SD cm	SD cm
$4^{2}/$	2	119	1 4					
5	0							
$5\ /_{12}$	7	119	5 2					
$6^{10}/$	37	126	4.2	7– 8	48	126	5 1	4 1
$7^{10}/_{12}$	55	132	4.9	8– 9	40	131	5 9	4.8
8 /	52	136	5 7	9–10	56	134	6 2	5 4
10	61	142	5.9	10–11	49	144	6 5	5.3
11	46	148	5 0	11–12	68	146	7 2	4.9
12	50	154	6.3	12–13	46	153	7 2	6 4
13	46	156	6.1	13–14	62	158	6 2	6 1
$13\ /_{12}$	24	162	5 8					
14	26	162	5.4	14–15	55	162	5 7	5 3
15	40	162	5 3	15–16	51	164	4 5	3 1
16	40	164	5.5	16–17	30	16	6 4	6 3
17	31	164	6 6	17–18	21	168	6 2	6.4
18	15	166	6 7	18–18 /	6	166	4 6	4 9
Total	532		5.6		532		6 2	5 4

height increment being approx. 5 cm. It was expected that the Danish children would be a few cm shorter than the children of the American series, as the assessment of their skeletal age showed that the boys as well as the girls were retarded by about 6 months in relation to the children of the Brush Foundation study. The difference in height gain is most marked during the years of the growth spurt, less marked for the more advanced ages. The boys of Dossing's material were an average of 4.0 cm shorter and the girls an average of 3.3 cm shorter than those of the present material. The standard deviations are of almost the same size in all materials.

Table 13 gives, for boys and girls, the mean height difference between the Brush Foundation material and the named Scandinavian materials.

If Key's study from 1891 concerning the height of 18 000 boys and girls

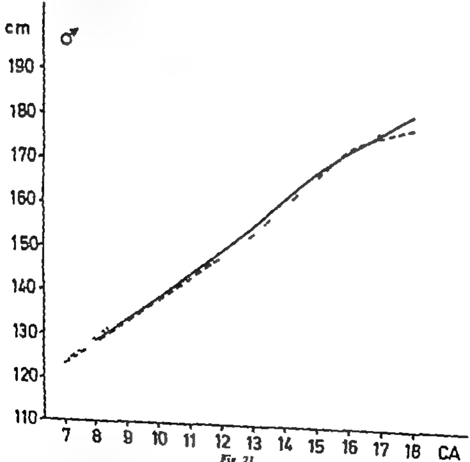

Fig. 21

Height in relation to chronological age for the boys of
the Brush Foundation material.
the present material.
Broman, Dahlberg & Lichtenstein's material.

Table 11

Height in relation to skeletal age and chronological age with standard deviations. SD indicates the standard deviation when the SA as well as the CA are constant.

Boys

SA (years)	Number	M cm	SD cm	CA (years)	Number	M cm	SD cm	SD* cm
5	4	123	3.3					
6	23	125	3 7					
7	41	128	4.5	7– 8	48	127	4.8	3 8
8	37	134	4 7	8– 9	[illegible]	130	4.8	4 0
9	43	136	4 6	9–10	57	138	4 9	4.5
10	41	142	5 4	10–11	48	142	6 7	5 0
11	37	147	6 7	11–12	48	146	6.7	5 8
$11^{6}/_{12}$	35	146	6.3					
$12^{6}/_{12}$	41	155	5 6	12–13	39	15[illegible]	7.5	5.5
13	23	158	4.9	13–14	52	161	7 1	4.9
$13\ /_{1}$	22	162	5.8					
14	54	168	6.9	14–15	56	165	8 4	6 4
15	17	172	6.9	15 16	33	169	8.7	7.8
$15^{6}/_{12}$	10	174	6.5					
16	9	172	6 8	16–17	27	174	7 3	6 4
17	21	176	6.4	17–18	15	179	6.5	6 7
18	13	181	5.3	$18–18\ /_{2}$	11	181	6 0	5 7
19	6	183	5.5					
Total	477		5.7		477		6.8	5 4

Table 12

Height in relation to skeletal age and chronological age with standard deviations. SD* indicates the standard deviation when the SA as well as the CA are constant.

Girls

SA (years)	Number	M cm	SD cm	CA (years)	Number	M cm	SD cm	SD* cm
$4^{9}/_{12}$	2	119	1 4					
5	0							
$5^{9}/_{12}$	7	119	5.2					
$6^{10}/$	37	126	4.2	7– 8	48	126	5 1	4 1
$7^{10}/$	55	132	4.9	8– 9	40	131	5.9	4.8
$8^{1}\ /_{12}$	52	136	5 7	9–10	56	134	6 2	5 4
10	61	142	5.9	10–11	49	144	6 5	5.3
11	46	148	5.0	11–12	68	146	7 2	4.9
12	50	154	6.3	1 –13	46	153	7 2	6 4
13	46	156	6.1	13–14	62	158	6 2	6 1
$13\ /_{12}$	24	162	5.8					
14	26	162	5 4	14–15	55	162	5 7	5 3
15	40	162	5.3	15–16	51	164	4 5	5 1
16	40	164	5.5	16–17	30	162	6 4	6 3
17	31	164	6.6	17–18	21	168	6 2	6 4
18	15	166	6.7	18–18 /	6	166	4 6	4 9
Total	532		5.6		532		6.2	5 4

Table 14
Height of Swedish boys 1950
(Abrahamson & Ernest 1954)

Age	Height cm	SD cm
10 years ($9^{1}/_{2}$–$10^{1}/_{2}$)	146.4	8.8
11 –	147.6	6.2
12 –	151.2	6.9
13	156.7	7.3
14	164.2	8.7
15	170.0	8.1
16	173.7	7.3
17	178.3	5.3
18	179.7	6.9

have not yet entered the adolescent growth spurt. These factors perhaps indicate that the value involves errors. Therefore, this age group should be left out in comparisons with other height tables. If the 11–17 year-old boys are compared with the corresponding age groups in the Brush Foundation material, the Swedish and American boys are seen to be of approximately the same height.

Falkner's height tables, worked out on the basis of 12 American height tables, show lower values than the Brush Foundation material. One of the 12 tables was set up by Meredith on the basis of investigations in the Iowa Child Welfare Research Station, the State University of Iowa 1930–1946. This set of tables is used in Nelson's Textbook of Pediatrics (1964). In the age range 7–17 years the boys of Meredith's material are an average of 1.7 cm and the girls an average of 2.6 cm shorter than the children of the Brush Foundation material.

Comparison of these height tables shows that the adolescent growth spurt is taking place ever earlier and that children in Scandinavia have not until recently approached the heights which had been attained by the children of the Brush Foundation material about 25 years ago.

Height in Relation to Skeletal Age

The curves in Figs. 23 and 24 illustrate height in relation to skeletal age for boys and girls.

The boys' curve runs a steeper course from skeletal age $11^{1}/_{2}$–15 years during which period the height gain is 8 cm per skeletal year. For the girls the curve is more even. Longitudinal studies have revealed that in boys the growth spurt occurs on the average from $12^{1}/_{2}$–15 years of age (chronological age). During this period they gain an average of 20 cm. In girls the growth spurt generally occurs 2 years earlier and is less marked than in the boys (Tanner). Although the present study is cross-sectional, it proved possible to visualize the adolescent growth spurt by relating height to skeletal age.

It may be noted that in Tables 11 and 12, giving the variation in heights with CA and SA respectively, chronological age is given in whole, completed years, (i.e. from one birthday to the next, 7 years meaning from the 7th until the 8th birthday) while skeletal ages indicate the nearest whole year.

The material was divided into half year groups: 7–$7^{1}/_{2}$ years, $7^{1}/_{2}$–8 years, etc., so that both whole, completed years and nearest whole years could be used to express chronological age. The tables most often state whole completed years for the following reasons. The material comprises children from municipal schools in Copenhagen.

Table 13

Average number of cm by which the children of the Brush Foundation material exceed various Scandinavian materials in height.

	Boys	Girls
Oslo *1960*	0.8 cm	1.6 cm
Denmark *1964*	2.2 –	2.8 –
Bergen 1956	2.7 –	3.6 –
Sweden *1938–1939*	2.6 –	3.3 –

from Stockholm is compared with the results of the present height analysis, it will be seen that boys and girls from grammar schools in the age range 7–17 years were then an average of 11 and 8 cm shorter.

The most recent Swedish height study is Abrahamson & Ernest's from 1954, but they studied only boys and only in the age range 10–18 years. The investigation was performed in 1950 on 871 boys in a Stockholm school. The result is shown in Table 14. A difference of only 1.2 cm between the 10-year-olds and 11-year-olds may seem surprising. Another striking factor is the high standard deviation for the 10-year-old boys who

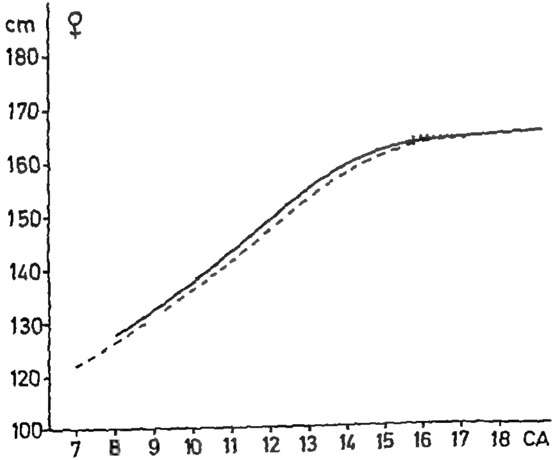

Fig. 2

Height in relation to chronological age for the girls of

the Brush Foundation material.

——— the present material.

– – – – Broman, Dahlberg & Lichtenstein's material.

Table 14

Height of Swedish boys 1950
(Abrahamson & Ernest 1954)

Age	Height cm	SD cm
10 years (9 1/2–10 1/2)	146.4	8.8
11 –	147.6	6.2
12	151.2	6.9
13	156.7	7.3
14	164.2	8.7
15	170.0	8.1
16 –	[illegible]	7.3
17	178.3	5.5
18	179.7	6.9

have not yet entered the adolescent growth spurt. These factors perhaps indicate that the value involves errors. Therefore this age group should be left out in comparisons with other height tables. If the 11–17 year-old boys are compared with the corresponding age groups in the Brush Foundation material, the Swedish and American boys are seen to be of approximately the same height.

Falkner's height tables, worked out on the basis of 12 American height tables, show lower values than the Brush Foundation material. One of the 12 tables was set up by Meredith on the basis of investigations in the Iowa Child Welfare Research Station, the State University of Iowa 1930–1946. This set of tables is used in Nelson's Textbook of Pediatrics (1964). In the age range 7–17 years the boys of Meredith's material are an average of 1.7 cm and the girls an average of 2.6 cm shorter than the children of the Brush Foundation material.

Comparison of these height tables show that the adolescent growth spurt is taking place ever earlier and that children in Scandinavia have not until recently approached the heights which had been attained by the children of the Brush Foundation material about 25 years ago.

Height in Relation to Skeletal Age

The curves in Figs. 23 and 24 illustrate height in relation to skeletal age for boys and girls.

The boys' curve runs a steeper course from skeletal age 11 1/2–15 years during which period the height gain is 8 cm per skeletal year. For the girls the curve is more even. Longitudinal studies have revealed that in boys the growth spurt occurs on the average from 12 1/2–15 years of age (chronological age). During this period they gain an average of 20 cm. In girls the growth spurt generally occurs 2 years earlier and is less marked than in the boys (Tanner). Although the present study is cross-sectional, it proved possible to visualize the adolescent growth spurt by relating height to skeletal age.

It may be noted that in Tables 11 and 12, giving the variation in heights with CA and SA respectively, chronological age is given in whole, completed years, (i.e. from one birthday to the next, 7 years meaning from the 7th until the 8th birthday), while skeletal ages indicate the nearest whole year.

The material was divided into half year groups: 7–7 1/2 years, 7 1/2–8 years, etc., so that both whole, completed years and nearest whole years could be used to express chronological age. The tables most often state whole completed years for the following reasons. The material comprises children from municipal schools in Copenhagen.

At present children cannot enter school until after their 7th birthday However the material included 3 children who had nevertheless started before their 7th birthday but these 3 children were left out of the analysis. In order not to have to exclude also all children aged 7–7 ½ years it seemed advisable to use whole completed years. Where it was necessary in order to compare with materials in which the chronological age is given in nearest whole years, this grouping was also used for the present material (Tables 7 and 8) The grouping by whole completed years is advantageous, as the shift of ½ year between the chronological age and skeletal age fits the fact that the present children were retarded by about 6 *months* in relation to the American children. Therefore boys of a chronological age of say 10 but not yet 11 years measure 142 cm and so do boys whose skeletal age is 10 years.

The standard deviations in Tables 11 and 12 indicate how much the *height* varies *for* a given *chronological* age and a given skeletal age. These tables also give the standard deviation which appears if the chronological age as well as the skeletal age are kept constant On the average, the SD is 5 4 cm for boys as well as for girls.

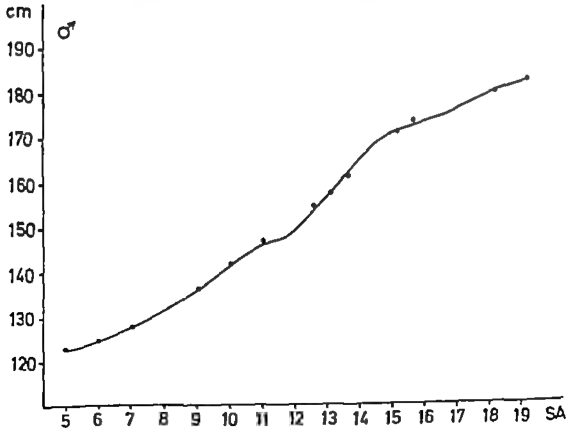

Fig 3
Height in relation to skeletal age for the boys of the present material.

The calculation was performed for those sub-groups which are obtained *when the material is grouped simultaneously into chronological six-month* groups and by skeletal age.

For the younger age groups the standard deviation is somewhat less pronounced than for the age groups which are in the *growth spurt*. The *average standard deviation corresponds* approximately to the variation in height found in adults. Broman, Dahlberg & Lichtenstein found, among men aged 20, a SD of 6.0 and for women 5.1 cm. These values are comparable with the 5.4 *cm*, since it may be assumed, *roughly* that the 20-year-old persons have reached skeletal maturity so that their SA is constant. This SD of 5.4 cm then is mainly due to an individual *variation independent* of age.

With a constant *SA* and a *varying* CA, the mean *SD* is 5.7 for boys and 5.6 cm for girls. With a constant CA and a varying SA, the increase in SD will be 19 % and 11 % respectively *making* 6.8 *cm for* boys and 6.2 *cm* for girls. This increase is greatest in the intermediate ages when growth is also fastest.

With a constant SA as well as CA, both boys and *girls* showed a *SD* of 5.4 cm, and with a *constant SA* and varying *CA* the SD was 5.7 for boys

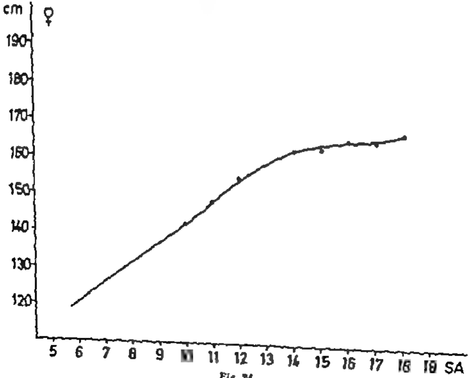

Fig 24

Height in relation to skeletal age for the girls of the present material.

At present children cannot enter school until after their 7th birthday However the material included 3 children who had nevertheless started before their 7th birthday but these 3 children were left out of the analysis. In order not to have to exclude also all children aged 7–7 ½ years, it seemed advisable to use whole completed years. Where it was necessary in order to compare with materials in which the chronological age is given in nearest whole years, this grouping was also used for the present material (Tables 7 and 8) The grouping by whole completed years is advantageous, as the shift of ½ year between the chronological age and skeletal age fits the fact that the present children were retarded by about 6 months in relation to the American children. Therefore boys of a chronological age of say 10 but not yet 11 years measure 142 cm and so do boys whose skeletal age is 10 years.

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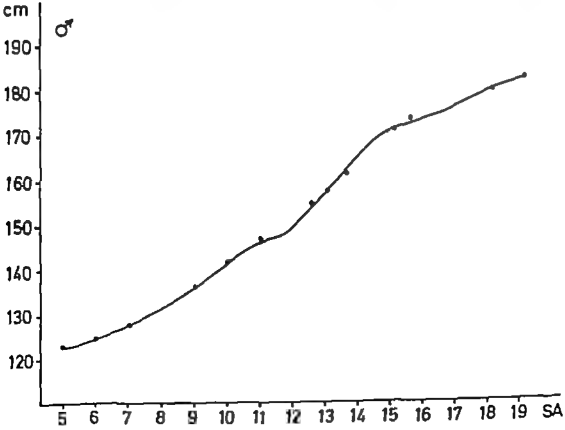

Fig 23

Height in relation to skeletal age for the boys of the present material

The calculation was performed for those sub-groups which are obtained when the material is grouped simultaneously into chronological six-month groups and by skeletal age.

For the younger age groups the standard deviation is somewhat less pronounced than for the age groups which are in the growth spurt. The average standard deviation corresponds approximately to the variation in height found in adults. Broman, Dahlberg & Lichtenstein found, among men aged 20, a SD of 6.0 and for women 5.1 cm. These values are comparable with the 5.4 cm, since it may be assumed, roughly that the 20-year-old persons have reached skeletal maturity so that their SA is constant. This SD of 5.4 cm then, is mainly due to an individual variation independent of age.

With a constant SA and a varying CA, the mean SD is 5.7 for boys and 5.6 cm for girls. With a constant CA and a varying SA, the increase in SD will be 19 % and 11 % respectively making 6.8 cm for boys and 6.2 cm for girls. This increase is greatest in the intermediate ages when growth is also fastest.

With a constant SA as well as CA, both boys and girls showed a SD of 5.4 cm, and with a constant SA and varying CA the SD was 5.7 for boys

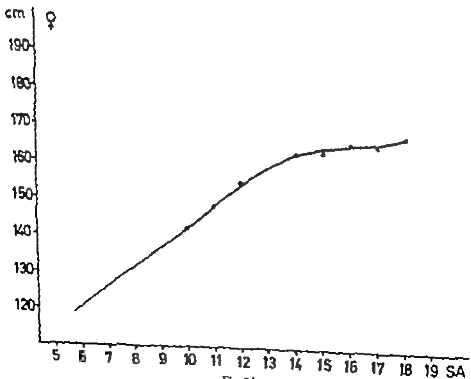

Fig. 24

Height in relation to skeletal age for the girls of the present material

At present children cannot enter school until after their 7th birthday How ever the material included 3 children who had nevertheless started before their 7th birthday but these 3 chil dren were left out of the analysis. In order not to have to exclude also all children aged 7–7 ½ years it seemed advisable to use whole com pleted years. Where it was necessary in order to compare with materials in which the chronological age is given in nearest whole years, this grouping was also used for the present material (Tables 7 and 8) The grouping by whole completed years is advanta geous as the shift of ½ year between the chronological age and skeletal age fits the fact that the present children were retarded by about 6 months in relation to the American children. Therefore, boys of a chronological age of say 10 but not yet 11 years meas ure 142 cm and so do boys whose skele tal age is 10 years.

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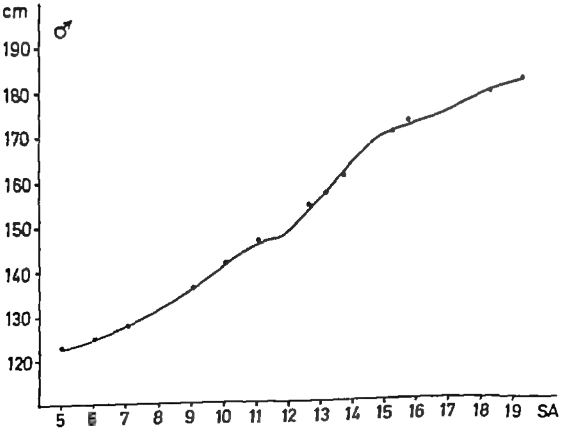

Fig 23
Height in relation to skeletal age for the boys of the present material

number n_1 and n_2 of observations in the two sub-groups.
When

$$w = \frac{n_1 \times n_2}{n_1 + n_2} \tag{1}$$

the average difference will be

$$\bar{d} = \frac{\Sigma\, w \times d}{\Sigma\, w} = \text{mean} \tag{2}$$

with the standard error

$$se < \bar{d} > = \frac{\sigma}{\sqrt{\Sigma\, w}} \tag{3}$$

were σ is the standard deviation of the heights in one sub-group.

It is apparent from Tables 15 and 16 that the difference in height, when skeletal age is shifted by 1 year and chronological age is constant, is 2.9 cm for boys aged 7–11 years, thereafter [illegible]1 cm up to the age of 14 and from 14 to 16 years of age 2.4 cm. With a constant skeletal age, the differences for a 1 year shift in chronological age are considerably lower. For the ages mentioned above the differences for boys are 2.3 cm, 2.1 cm and 1.8 cm.

For the girls the difference, with constant CA and a 1-year shift in SA, was 3.4 cm for the age 7–10 years, 3.8 for the age 10–13 years, and for the older ages 0.8 cm. With a constant SA and a 1 year shift in CA, the corresponding age groups showed differences of 3.0 cm, 2.0 cm, and 0.3 cm.

The individual differences carry a fairly marked uncertainty and therefore vary appreciably from age to age. As a whole, however they are positive both when SA and when CA are

Table 15

Change in height when the skeletal age or chronological age is shifted 1 year (the other parameter being kept constant)

Boys

Skeletal age increased			Chronological age increased		
Initial SA (years)	Difference cm		Initial CA (years)	Difference cm	
[illegible]	4.0				
6	1.4				
7	4.9		7–8	1.6	
8	0.9		8–9	3.8	
9	2.8	2.9±0.7	9–10	3.0	2.3±0.8
10	3.0		10–11	0.7	
11	4.2		11–12	2.1	
12[illegible]	5.5	6.1±0.9	12–13	4.5	2.1±1.0
13	9.0		13–14	0.1	
14	2.2		14–15	−1.9	
15	−0.4	2.4±1.3	15–16	[illegible]	1.8±1.2
16	4.6		16–17	2.5	
17	6.1				
18	2.9				
Total		3.5±0.4			2.1±0.6

and 5 6 for girls, i.e. an increase of only 6 % and 4 %. This indicates that height depends more upon SA than upon CA.

Simmons (1944) relating the height measurements from the Brush Foundation material to chronological age as well as to skeletal age, found for most ages that the SD with a constant skeletal age was 20 % lower than with a constant chronological age. This corresponds approximately to the findings in the present material. For a few ages, however she found a reduction of 40 %. Bayley (1943) also found a closer relationship between height and skeletal age than between height and chronological age.

If instead of height itself the height could be expressed in per cent of adult height (Bayley 1943) the individual variation in height could have been almost approximately eliminated. This would also have given a greater difference between the standard deviations appearing when either the CA or the SA is constant

In the intermediate age groups the ratio between the standard deviations might be expected to be greater Bayley (1943) who demonstrated a high correlation between height and SA worked out tables, in collaboration with Pinneau (1952) showing the percentage of adult height to which various skeletal ages correspond On the basis of these tables, the adult height may be predicted when a child's skeletal age, height and chronological age are known. The accuracy expressed in SD is 2.5 cm if the skeletal age differs by 1 SD or less from the norm. The more advanced or retarded the skeletal maturation the less accurate the prediction. The accuracy decreases with decreasing age, the distance" from the 100 % which represents adult height increasing The tables are not applicable to children younger than 6 years.

The present results do not permit a definite evaluation of the dependence of growth upon skeletal age. Therefore an attempt was made to determine the alteration in average height when the SA is shifted 1 year while the CA is constant and to compare the change in height when the CA is shifted 1 year and the SA remains constant.

This method has the advantage of being applicable also to criteria of maturation such as the onset of menarche for which no continuous measurements are available.

The procedure was as follows The material was divided simultaneously by skeletal age, determined by the Greulich & Pyle method, and into chronological half year groups. For each of the resulting sub-groups the mean value for height was calculated In order to ascertain the importance of a shift in skeletal age from e.g 9 to 10 years, the author picked out those chronological ages for which observations were available for both skeletal ages, and calculated the difference between the mean values of heights for the two skeletal ages. It was found that these differences did not depend in any essential degree upon the chronological age for which they were calculated Therefore a common average was calculated. In calculating this average the weight w of the individual differences is given in relation to the

number n_1 and n_2 of observations in the two sub-groups.

When

$$w = \frac{n_1 \times n_2}{n_1 + n_2} \qquad (1)$$

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5	2.0				
6	1.4				
7	4.9		7–8	1.6	
8	0.9	2.9±0.7	8–9	3.8	2.3±0.8
9	2.8		9–10	3.0	
10	3.0		10–11	0.7	
11	4.2		11–12	2.1	
12[illegible]	5.3	6.1±0.9	12–13	4.5	2.1±1.0
13	9.0		13–14	0.1	
14	2.1		14–15	−1.9	
15	−0.4	2.4±1.3	15–16	8.3	1.8±1.2
16	4.6		16–17	2.3	
17	6.1				
18	2.9				
Total.		3.3±0.4			2.1±0.6

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skeletal as well as height age. Thereafter the terms which are specific to skeletal and height age respectively p and l depend upon biological factors, and and m indicate the error of measurement of the two determinations.

When SA varies and CA is constant, shift in SA of one unit will show an average distribution on the three quantities h, p and e in relation to their variances

$$\sigma_h^2,\ \sigma_p^2 \text{ and } \sigma_e^2.$$

In other words, when SA is changed by one unit, h and thus also HA will, on the average change

$$\frac{\sigma_h^2}{\sigma_h^2+\sigma_p^2+\sigma_e^2} \text{ units.}$$

With constant SA, the quantities on the right side in equation (5) will keep each other in equilibrium, so that when CA is changed by one unit, h+p+e must alter correspondingly in the opposite direction, and the change will be distributed on h, p, and in the same ratio as previously assuming that CA may be considered as being equally distributed within the age interval with which we are concerned.

The change in HA will correspond to the alteration in CA+h, which again corresponds to the alteration in p+e. Thus, HA will alter by

$$\frac{(\sigma_p^2+\quad^2)}{(\sigma_h^2+\sigma_p^2+\sigma_e^2)} \text{ units.}$$

Consequently when SA and CA respectively alter by one unit, the corresponding changes in HA will be rated as

$$q=\frac{\sigma_h^2}{\sigma_p^2+\sigma_e^2} \tag{7}$$

or since the intervals may be considered small, the changes in height measured in cm will have the same ratio.

I Chapter 6 the biological variation was estimated to be

$$\sigma_h^2+\sigma_p^2=110 \text{ months}$$

and the error of measurement

$$\sigma_e^2=39 \text{ months.}$$

Using (6)

$$\sigma_p^2=\frac{110-39\,q}{1+q}$$

When inserting the mean value q = 1 7

$$\sigma_p^2=13 \text{ months, or only } / \text{ of } \sigma\ ^2$$

Of course, these are uncertain estimates, but they do show that the dependence of height upon CA, with constant SA, is due mainly to difficulties in determining SA.

M. Nykahn.

Table 16

Change in height when the skeletal age or chronological age is shifted 1 year (the other parameter being kept constant)

Girls

Skeletal age increased			Chronological age increased		
Initial SA (years)	Difference cm		Initial CA (years)	Difference cm	
$5\ /_{12}$	5.5				
$6^{10}/$	3 6		7– 8	3 4	
$7^{10}/_{12}$	3 7	3 4±0.7	8– 9	1 0	3 0±1 0
$8^{10}/_{12}$	2.6		9–10	6 4	
10	4.3		10–11	0.5	
11	4 6	3.8±0 7	11–12	2.6	2.0±1 0
12	? 4		12–13	1 4	
13	1 3		13–14	−0.6	
14	0.9	0.8±0 7	14–15	−1.2	0.3±0.8
15	0.4		15–16	1 6	
16	−0 4		16–17	−0.4	
17	2.1				
Total		2 7±0 4			1 6±0 5

changed. *The means differ significantly from 0*

Here, and in the following the significance will be evaluated by the aid of

$$u = \frac{\text{difference}}{\text{standard error of difference}}$$

(When the CA is changed u takes the value 3 5*** for boys and 3 2** for girls)

The difference will also be significantly greater when the SA is *changed than when the CA is changed* For boys u = 2 3* and for girls 2 0* Calculation of a common u value for *the higher age groups gives u = 2.5**

The ratio of the two differences averages 1 7 for boys as well as girls.

A given skeletal age then affords a better estimate than a given chronological age of which percentage of its final height a child has attained

The reason why the correlation between height and skeletal maturation is not complete may be errors in determining skeletal age, but may also be that children who are skeletally retarded may have attained at a given skeletal age, a higher percentage of their adult height than advanced children of the same skeletal age (Bayley 1943)

Theoretically this may be set up as follows Assuming that skeletal ge as well as height age may be expressed as the sum of four independent quantities

$$SA = CA + h + p + e \qquad (5)$$

and

$$HA\ (\text{height age}) = CA + h + l + m \qquad (6)$$

The first term on the right indicates that the average course of the skeletal and height age will correspond t the chronological (CA) The following terms ndicate deviations from this average course First, common term h, comprising the factors which nfluence

skeletal as well as height age. Thereafter the terms which are specific to skeletal and height age respectively p and l depend upon biological factors, and and m indicate the error of measurement of the two determinations.

When SA varies and CA is constant, a shift in SA of one unit will show an average distribution on the three quantities h, p and in relation to their variances

$$\sigma_h^2, \sigma_p^2 \text{ and } \sigma^2$$

In other words, when SA is changed by one unit, h and thus also HA will, on the average change

$$\frac{\sigma_h^2}{\sigma_h^2 + {}_p^2 + \sigma_a^2} \text{ units.}$$

With constant SA, the quantities on the right side in equation (5) will keep each other in equilibrium, so that when CA is changed by one unit, h+p+a must alter correspondingly in the opposite direction, and the change will be distributed on h, p, and in the same ratio as previously assuming that CA may be considered as being equally distributed within the age interval with which we are concerned.

The change in HA will correspond to the alteration in CA+h, which again corresponds to the alteration in p+a. Thus HA will alter by

$$\frac{(\sigma_p^2 + {}^2)}{(\sigma_h^2 + \sigma_p^2 + \sigma^2)} \text{ units.}$$

Consequently when SA and CA respectively alter by one unit, the corresponding changes in HA will be rated as

$$q = \frac{\sigma_h^2}{\sigma_p^2 + \sigma_c^2} \qquad (7)$$

or since the intervals may be considered small, the changes in height measured in cm will fan the same ratio.

In Chapter 6 the biological variation was estimated to be

$$\sigma_h^2 + \sigma_p^2 = 110 \text{ months}$$

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$$\sigma_p^2 = \frac{110 - 39\,q}{1+q}$$

When inserting the mean value q = 1 7

$$\sigma_p^2 = 13 \text{ months, or only } 1/\ \text{ of } \sigma^2$$

Of course, these are uncertain estimates, but they do show that the dependence of height upon CA with constant SA, is due mainly to difficulties in determining SA.

M. Nyholm.

Chapter 8

Menarche

Previous Studies of Age at Menarche

The most important Danish study concerning the age at menarche is Bojlén Rasch & Weis Bentzon's (1954). In a material of 17,589 girls and young women aged 9 to 25 years attending schools, continuation courses, and evening schools in Copenhagen they collected data as to whether or not the pupil was menstruated and the time of menarche. This study was performed from 1948 to 1950.

The material was grouped by age into three month groups, but in the groups younger than 13 and older than 16 into six month groups. For each group the percentage of girls who were menstruated was calculated. The average age of menarche was found to be 13.8 years ± 1.0 SD. The same paper gives a list of other Danish menarche studies.

Author	Year	Number of patients	Age at menarche
Ravn	1850	3840	15.84
Hannover	1865	2129	16.91
Helms	1914	1000	ca. 15
Clausager Madsen & Ytting	1942	478	14.73
Gortz	1945	12..5	13
Auken	1951	314	14.2

Lundwall (1959) calculated on the basis of 2076 records from the Maternity Departments of the University Hospital Copenhagen for 1956 that the age at menarche was 14.3 years.

Evidently there is a tendency for the menarche to occur at an ever earlier age. However the values are not directly comparable, because the data on which they are based have been collected and analyzed in widely different ways.

Ravn (1850) collected his data mainly from the records of the University Maternity Department. Hannover's (1865) material comprised women of all ages admitted to Copenhagen hospitals during the period 1850–1865. Helms (1914) asked female patients aged 18–42 years admitted to a tuberculosis sanatorium about their age at the time of their first menstrual period.

Clausager Madsen & Ytting (1942) obtained their data from women who who had passed the menopause. Gortz (1945) studied the age at menarche in schoolgirls aged 10–15 by asking after which birthday the first menstrual period had occurred.

Some inaccuracy must be assumed to attach to the data concerning the time of menarche, as they depend upon

Tabl 17

Menarche studies in Finland, Norway and Sweden.

Author	Year	Material	Method	Number	Age at menarche
Malmio, Finland	1920	Gynaecological and obstetrical patients	Recollection method	28,811	16.0
Schiøtz, Norway	1930	Schoolgirls	Status quo method	2,008	14 03
Samuelson, Sweden	1943	Gynaecological patients	Recollection method	515	15 0
Lenner, Sweden	1944	Gynaecological and obstetrical patients	Recollection method	2,000	14 48
Simell, Finland	1952	Healthy women	Recollection method	3,057	14.25

the subjects memory Presumably the most accurate data are supplied by fairly young women.

The ages stated above are based upon information from women of widely different ages, and this must be taken into consideration when making any comparisons.

A further difficulty is that some ages have been calculated for normal materials and others for hospitalized women.

Schiøtz (1919) calculated the age at menarche for girls in Oslo, Norway partly on the basis of data concerning the time of the first menstruation and partly on the basis of information whether or not menstruation had started (recollection method and *status quo* method) The latter method gave a higher age and he pointed out that this method was preferable, because often girls are not sure of the age at the 1st menstruation, while they always know whether or not they are menstruated.

Quaade (1955) calculating the average age at menarche in 509 school-

Table 18

Recent menarche studies based upon longitudinal investigations or upon the *status quo* method.

Author	Year	Method and period of study	Number	Age at menarche
Simmons & Greulich Brush Foundation study U S A	1943	Longitudinal study 1931 1942	200	12 6
Reynolds & Wines, Fels Institute study U S.A	1948	Longitudinal study 1938–1946	49	12.9
Bojlén, Rasch & Weis Bentzon, Denmark	1954	Status quo method 1948–1950	17,985	13.8
Wilson & Sutherland, South England	1961	Status quo method	2,180	13.2

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Previous Studies of Age at Menarche

The most important Danish study concerning the age at menarche is Bojlén, Rasch & Weis Bentzon's (1954). In a material of 17 589 girls and young women aged 9 to 25 years attending schools, continuation courses, and evening schools in Copenhagen they collected data as to whether or not the pupil was menstruated and the time of menarche. This study was performed from 1948 to 1950.

The material was grouped by age into three month groups, but in the groups younger than 13 and older than 16 into six month groups. For each group the percentage of girls who were menstruated was calculated. The average age of menarche was found to be 13 8 years ± 1 0 SD. The same paper gives a list of other Danish menarche studies.

Author	Year	Number of patients	Age at menarche
Ravn	1850	3840	15 84
Hannover	1865	2129	16.91
Helms	1914	1000	ca. 15
Clausager Madsen & Ytting	1942	478	14 73
Gortz	1945	1225	13
Auken	1951	314	14.2

Lundwall (1959) calculated on the basis of 2076 records from the Maternity Departments of the University Hospital Copenhagen for 1956 that the age at menarche was 14 3 years.

Evidently there is a tendency for the menarche to occur at an ever earlier age. However the values are not directly comparable, because the data on which they are based have been collected and analysed in widely different ways.

Ravn (1850) collected his data mainly from the records of the University Maternity Department. Hannover's (1865) material comprised women of all ages admitted to Copenhagen hospitals during the period 1850–1865. Helms (1914) asked female patients aged 18–42 years admitted to a tuberculosis sanatorium about their age at the time of their first menstrual period.

Clausager Madsen & Ytting (1942) obtained their data from women who who had passed the menopause. Gortz (1945) studied the age at menarche in schoolgirls aged 10–15 by asking after which birthday the first menstrual period had occurred.

Some inaccuracy must be assumed to attach to the data concerning the time of menarche, as they depend upon

Table 17

Menarche studies in Finland, Norway and Sweden.

Author	Year	Material	Method	Number	Age at menarche
Malmio, Finland	1920	Gynaecological and obstetrical patients	Recollection method	28 811	16.0
Schiøtz, Norway	1930	Schoolgirls	Status quo method	2,008	14.03
Samuelsson, Sweden	1943	Gynaecological patients	Recollection method	513	15 0
Lauer, Sweden	1944	Gynaecological and obstetrical patients	Recollection method	2,000	14 48
Simell, Finland	195.	Healthy women	Recollection method	3,057	14 25

the subjects memory Presumably the most accurate data are supplied by fairly young women.

The ages stated above are based upon information from women of widely different ages, and this must be taken into consideration when making any comparisons.

A further difficulty is that some ages have been calculated for normal materials and others for hospitalized women.

Schiøtz (1919) calculated the age at menarche for girls in Oslo, Norway partly on the basis of data concerning the time of the first menstruation and partly on the basis of information whether or not menstruation had started (recollection method and *status quo* method) The latter method gave a higher age and he pointed out that this method was preferable, because often girls are not sure of the age at the 1st menstruation, while they always know whether or not they are menstruated.

Quaade (1955) calculating the average age at menarche in 509 school-

Table 18.

Recent menarche studies based upon longitudinal investigations or upon the *status quo* method

Author	Year	Method and period of study	Number	Age at menarche
Simmons & Greulich Brush Foundation study U. S. A	1943	Longitudinal study 1931 1942	200	12 6
Reynolds & Wines, Fels Institute study U S A	1948	Longitudinal study 1938–1948	49	12.9
Bojlén, Rasch & Weis Bentzon, Denmark	1954	Status quo method 1948–1950	17,985	13 8
Wilson & Sutherland, South England	1961	Status quo method	2,180	13.2

girls by the same method as Schiøtz and Bojlén Rasch & Weis Bentzon found the age to be 13 65 years.

For comparison, Table 17 gives the age at menarche in other Scandinavian countries.

The age at menarche is higher in rural than in urban districts and higher in poor social strata (Ravn, Hannover Schiøtz, Simell 1952)

Lennér (1944) calculated that the age at menarche had fallen by 10 days for each of the past 50 years. According to Tanner the age at menarche has fallen by 4 months per decade. Lundwall made a similar finding in Denmark From 1860–1870 until 1956 the age at menarche for women admitted to the Maternity Departments of the University Hospital in Copenhagen had fallen from 17 0 to 14.3 years.

In analysing the age at menarche correct results may be obtained partly by the *status quo* method and partly by collecting data from longitudinal studies in which the exact time of the menarche has been recorded.

Som recent studies, carried out by these methods, are listed in Table 18

Previous Studies of the Relation Between Skeletal Age and Menarche

Only a few studies have dealt with the relation between skeletal age and the onset of the menarche. Simmons & Greulich (1943) investigated the time of menarche in 200 girls of the Brush Foundation study The average age at menarche proved to be 12 6 years or $12^7/_{12}$ years. The age varied from 122 to 183 months, i.e. by 61 months.

The average skeletal age, assessed by Todd's atlas, was 13 1 years at menarche. This difference between skeletal age and chronological age (13 1–12.6) of 6 months at menarche is due to the fact that the children upon whom Todd based his atlas were skeletally retarded by about 6 months compared with the Brush Foundation children

The skeletal age ranged from 144 to 174 months, i.e. it varied by 30 months or by only half the period found for the chronological age.

The standard deviation of CA at menarche was ± 12 75 months, while the standard deviation of SA was only ± 5.34 months.

In a longitudinal study of 36 girls Hansman & Maresh found the chronological age at menarche to be 13 09 years ± 1 15 SD while the skeletal age at menarche was 12 96 ± 0.58 SD Accordingly the SD of the SA at menarche is only half the SD of the CA at menarche.

Shuttleworth (1937) who gave particular attention to the relation of the menarche to the growth spurt, plotted groups of girls with different ages at menarche against their skeletal ages. It is apparent from his curves that the standard deviation of chronological age is twice the standard deviation of skeletal age at menarche

Age at Menarche in Present Material

Table 19 and Fig 25 show how large a percentage of the girls had reached

Table 19

Percentage of girls who had reached menarche in relation to chronological age and skeletal age.

CA (years)	Number	Menarche in	%		SA (years)	Number	Menarche in	%
10 –10½	29	0	0		10	61	1	2
10½–11	20	0	0					
11 –11½	36	2	5	6	11	46	2	4
11½–12	32	2	6					
[illegible] –12½	23	7	30	22	[illegible]	50	9	18
12½–13	23	3	13					
[illegible] –13½	25	16	64	66	13	46	23	50
13½–14	37	25	67		13½	24	23	94
14 –14½	29	26	89	85	14	26	25	96
14½–15	26	21	82					
15 –15½	32	30	94	96	15	40	39	97
15½–16	19	19	100					
16 –16½	9	9	100	100	16	40	40	100
16½–17	21	21	100					
17 –17½	15	15	100	100	17	31	31	100
17½–18	8	[illegible]	100					
18 –18½	8	8	100		[illegible]	15	15	100

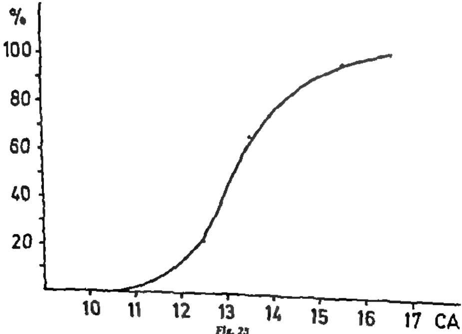

Fig. 25.

Percentage of girls who had reached menarche in relation to chronological age (present material)

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Age at Menarche in Present Material

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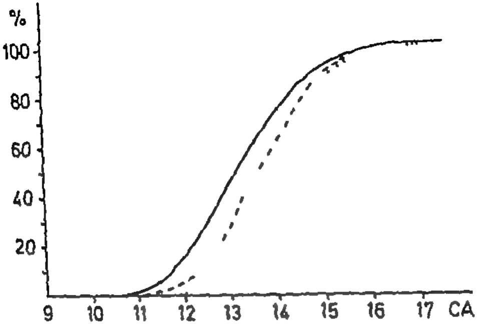


Fig 27

Percentage of girls who had reached menarche in relation to chronological age in

Boldsen, Rasch & Wels Benton material.
Quaade's material, and
— — the present material

1 year found in the earlier material.

The mean found in the present material is 8 months higher than that of the Brush Foundation material. This accords with the fact that in respect to height and skeletal maturation too the Danish material is about half a year retarded compared with the American material.

Age at Menarche in Relation to Skeletal Age in Present Material

Fig. 28 and Table 19 give the percentage of girls who had reached menarche in relation to skeletal age.

From the estimated cumulative distribution curve in Fig 28 the distribution curve was calculated and plotted as shown in Fig 29 The shape of this curve, like that in Fig. 26 is more illustrative, as the area within a given age interval represents the percentage of girls who attain menarche within this period. (Where the cumulative distribution curve ascends abruptly it is difficult to decide how far up the distribution curve will reach)

The curve shows that the earliest menarche occurs at a skeletal age of *10* years. At the outset the curve ascends slowly thereafter very abruptly in order suddenly to flatten out at skeletal age 13 ¹/₂ at which only 5 % had not started menstruating. Of

menarche at the different ages. The curve in Fig 25 has the same shape as those drawn on the basis of Bojlén Rasch & Weis Bentzon s and Quaade s menarche studies in Fig 27 The first onsets are at the age of 11 Initially the increase in per cent is slow there after faster around the age of 13 and at the age of 15 $^1/_2$ years 95 % of the girls had reached menarche. A distri bution like this is very like the normal cumulative distribution curve. In a large material Bojlén Rasch & Weis Bentzon demonstrated that this distri bution approximately fits the age at menarche. When the percentages were plotted on a probit diagram, the points in this material too were grouped along a straight line.

If the cumulative distribution curve is converted to a distribution curve, it proves to be the even symmetrical curve shown in Fig 26 Calculation of mean and standard deviation gives the age at menarche 13$^1/_4$ years ± 1$^1/_4$ year with the standard error se ± 0 24 year

The mean is about 6 months lower than in Bojlén, Rasch & Weis Bent zon s material which was collected about 15 years earlier A fall in the age at menarche in this order was to be expected since as previously stated the age at menarche in Europe has dropped during the past century by about 4 months per decade (Tanner) The mean differs significantly from that found by Bojlén Rasch & Weis Bentzon The standard deviation does not differ significantly from that of

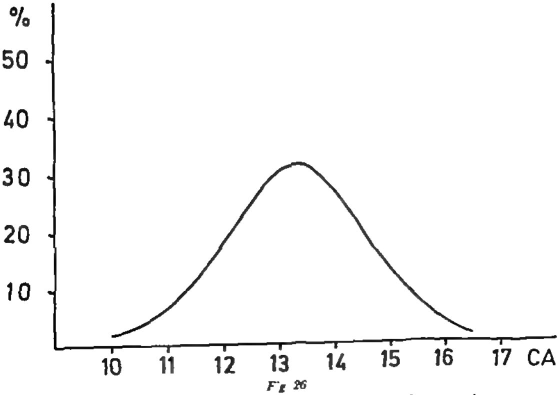
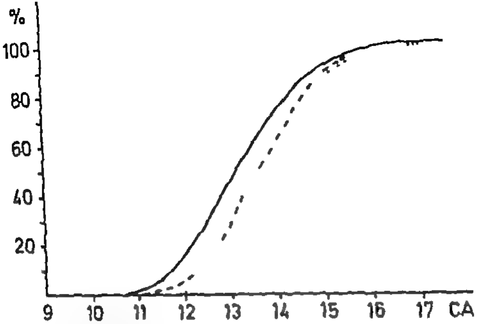


Fig 26

Distribution curve showing the percentage of girls reaching menarch in relation to chronological age (present material)



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course, this distribution cannot be approximated to a normal distribution.

This peculiar shape of the curve shows that the majority of the girls start menstruating within a much shorter time interval calculated in skeletal years than calculated in chronological years. 80 % of the girls reach their menarche in the course of $2^1/_4$ skeletal years, while 80 % reach their menarche in the course of about 4 calendar years.

This indicates a greater positive correlation between skeletal age and menarche than between chronological age and menarche. This aspect was investigated in further detail by comparing as for height how the percentages vary when CA and SA respectively is increased by 1 year However this comparison is more uncertain now that we are dealing with percentages and not with continuous measurements. But the method ought to be sufficient to estimate the ratio of the changes which take place when CA and SA respectively is shifted

The formulae for the weights (w) of the differences, the mean difference and standard error of the mean differences are the same as (1) (2) and (3) for the heights.

The standard deviation σ included in formula (3) is here

$$\sigma = \sqrt{h\ (100 - h)} \qquad (4)$$

where h is the frequency of the theoretical percentage of menarche which has occurred in the age group concerned

This value is not known, but in order not to underestimate σ and there

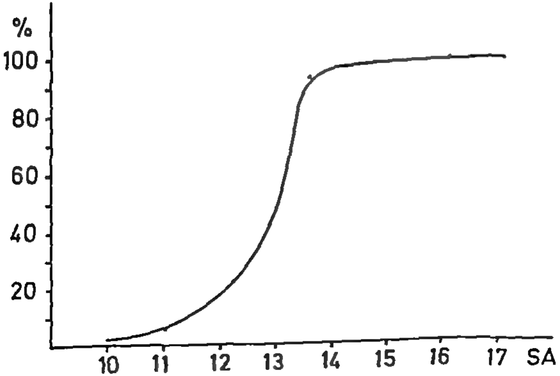

Fig 28

Percentage of girls who had reached menarche in relation to skeletal age (present material)

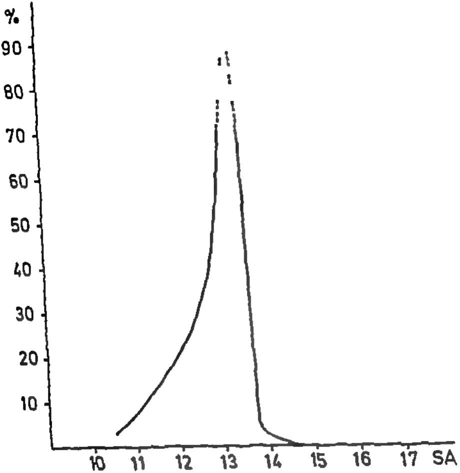

Fig 29

Distribution curve illustrating the percentage of girls reaching menarche in relation to skeletal age (present material)

by the uncertainty of the differences, h is fixed at 50, so that σ attains its maximum value $= 50$. In most cases, however the true value of σ cannot be much lower

In these calculations the author considered only those age groups where the greatest increase in menarche percentage from year to year occurs. For chronological age, whole-year age groups were used in order to procure sufficiently large numbers. The results are presented in Table 20

The change in the percentage of girls who had reached menarche is clearly greater when SA than when CA increases. The average values are 25.4 % $\pm$ 7.0 and 5.3 % $\pm$ 6.4 respectively The latter change is not significantly different from 0 ($u = 2.1$)

course, this distribution cannot be approximated to a normal distribution.

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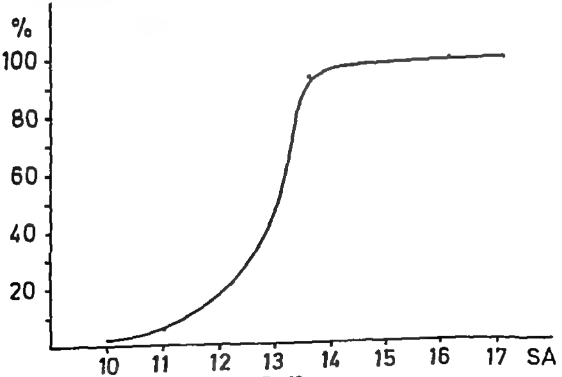

Fig 28

Percentage of girls who had reached menarche in relation to skeletal age (present material)

Present Study of Breast Maturation and Comparison with Previous Findings

Fig 30 illustrates *breast maturation in relation to chronological age* The curves were plotted on the basis of the values from Table 21 The curves, largely parallel, indicate the percentage of girls who have, at various chronological ages, attained stage II stage III and stage IV of breast maturation.

Breast maturation starts in a few per cent of the cases at the age of 8 Initially the curve ascends slowly then rather abruptly at the age of 10–11 years, and at 12 years of age breast maturation is in progress in 90 %

The development from stage II to IV occurs, on the average, from about $10^3/_4$ years to about $13^1/_2$ years of age, i.e. it takes about 3 years. In cases where breast maturation starts late, be cause of late puberty the development from stage II to stage IV takes about 4 years. Plotting of the points from

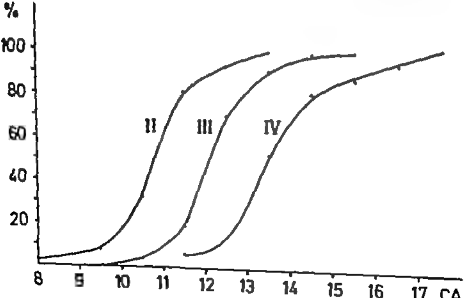

Fig 30

Percentage of girls who had attained stages II, III and IV of breast maturation in relation to chronological age (present material)

Table 20

Change in the percentage of girls who had reached menarche when the skeletal age or the chronological age is increased by 1 year Chronological age given in whole completed years.

Sk letal age held constant		Chronological ge held constant	
CA Increased	Difference in %	SA Increased	Difference in %
from 11 to 12 years	+ 2 1	from 11 to 12 years	+12.2
from 1 [illegible] 13 years	+16.4	from 12 to 13 years	+23 4
from 13 to 14 years	+ 0 7	from 13 to 14 years	+40 7
Total	+5 3 ± 6 4	Total	+25 4 ± 7 0

Conclusion

From this it is distinctly apparent that a change in skeletal age is of a decisive and far greater importance to the occurrence of menarche than is an increase in the chronological age, proving that skeletal maturation is better suited than chronological age as a measure of biological age. It may be assumed that the factors (probably hormonal) which determine the onset of menstruation are partially identical with those which regulate skeletal maturation.

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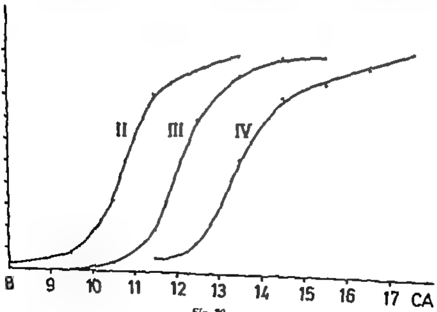

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Percentage of girls who had attained stages II III and IV of breast maturation in relation to chronological age (present material)

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Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 11 to 12 years	+ 2.1	from 11 to 12 years	+12.2
from 12 to 13 years	+16.4	from 12 to 13 years	+23.4
from 13 to 14 years	+ 0.7	from 13 to 14 years	+40.7
Total	+5.3 ± 6.4	Total	+23.4 ± 7.0

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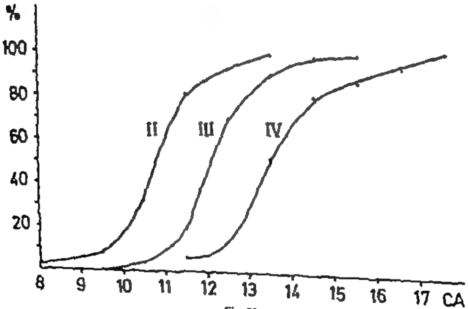

Fig. 30

Percentage of girls who had attained stages II, III, and IV of breast maturation in relation to chronological age (present material)

Table 21

Percentage of girls who had attained stages II III and IV of breast maturation in relation to SA and CA.

SA	Number	Stage II	%	Stage III	%	Stage IV	%	CA	Number	Stage II	%	Stage III	%	Stage IV	%
$6^{1}/_{1}$	37	1	3	0	0	0	0	7– 8	48	0	0	0	0	0	0
$7^{1}/_{12}$	55	2	4	0	0	0	0	8– 9	40	3	7	0	0	0	0
$8^{1}/_{12}$	52	6	12	0	0	0	0	9–10	56	4	7	0	0	0	0
10	61	28	46	1	2	0	0	10–11	49	16	32	2	4	0	0
11	46	19	78	11	24	1	2	11–12	68	55	81	13	19	4	6
12	50	48	96	33	66	6	12	12–13	46	43	92	32	70	5	11
13	46	46	100	43	93	19	43	13–14	62	61	99	56	90	32	52
$13^{1}/_{2}$	24	24	100	24	100	19	76								
14	26	26	100	26	100	20	77								
15	40	40	100	40	100	36	90	14–15	55	55	100	54	98	44	80
16	40	40	100	40	100	37	93	15–16	51	51	100	50	98	44	86
17	31	31	100	31	100	31	100	16–17	30	30	100	30	100	28	93
18	15	15	100	15	100	15	100	17–18	21	21	100	21	100	21	100
								18–$18^{1}/_{2}$	6	6	100	6	100	6	100

Table 22

Chronological age t which the various stages [illegible] breast maturation occur

Author	Year of publication	Longitudinal/cross-sectional study	Number	Years of study	Stages		
Reynolds & Wines	1948	Longitudinal	49	1938–46	II 10.8±1.1	IV 12.2	V 13.7
Harmann & Mareth	1961	Longitudinal	36	unknown	II 11.3±1.1		
Quesada	1955	Cross-sectional	509	1951	II 10[illegible]/12–11[illegible]/12	III 11[illegible]/12–12[illegible]/12	IV 12[illegible]/12–13[illegible]/12
Present study		Cross-sectional	532	1964	II 10.6±1.1	III 11.8	IV 13.5

Stages which, according to the description, correspond largely to each other are placed in the same column even though they have not always been given the same designation

curve II (Fig. 30) in a probit diagram gave an approximately straight line, i.e. the distribution was practically normal. Reading of this diagram gave a mean of 10.8 years, with a standard deviation of 1.1 year. The distribution curve is shown in Fig. 31.

For comparison, Table 22 gives the chronological ages at which the various stages of breast maturation had occur-

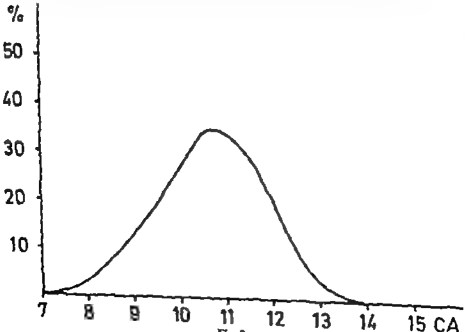

Fig. 3

Distribution curve showing the percentage of girls attaining stage II of breast maturation in relation to chronological age (present material)

red in previous studies. The stages which according to the description correspond largely to each other are placed below each other in the same columns, even though they have not always been given the same designation. In Quaade's (1955) as well as in the present study the method of Stratz was used in assessing the stage of breast maturation. The results are very similar. The standard deviations in Reynolds & Wines and in Hansman & Maresh investigations are identical with those in the present material. Breast maturation was not examined in the Brush Foundation study.

Plotting of the *breast maturation* found in the present study against *skeletal age* gives, as for the chronological ages, three almost parallel curves, representing breast maturation of stages II, III, and IV (Fig. 32). However, breast maturation usually starts at skeletal age 10.2 years, while for the chronological age it was 10.8 years. This is possibly because the children of the present material were retarded by about 6 months in relation to those of the Brush Foundation material. The development of the breast from stage II to IV takes an average of about 2 ½ years in terms of skeletal age.

Conversion of the curve representing stage II to a distribution curve shows an approximately normal distribution (Fig. 33). According to a probit diagram the mean was 10.2 and the standard deviation 1.1 year. In other words, the standard deviation is in the same range as for the chronological ages. Therefore, the correlation between

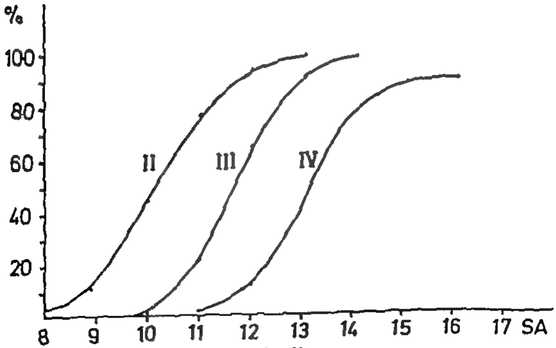

Fig. 32

Percentage of girls who had attained stages II, III and IV of breast maturation in relation to skeletal age (present material)

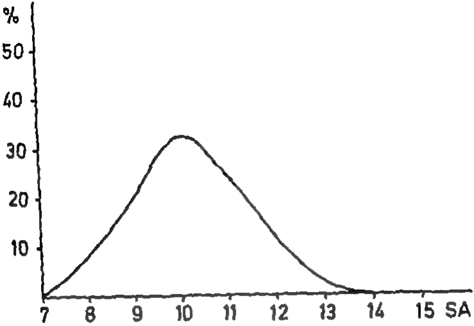

Fig 33

Distribution curv showing percentage of girls attaining stage II of breast maturation in relation to skeletal age (present material)

breast maturation and SA cannot be expected to be much higher than between breast maturation and CA. Hansman & Maresh, just like the present author found a standard deviation for stage II breast maturation of 1.1 year for CA as well as for SA.

To assess further the correlation between breast maturation and chronological age and between breast maturation and skeletal age, the author investigated, as for the menarche, the increase in the percentage of girls with incipient breast maturation (stage II)

Table 22.

Change in the percentage who attained stage IV of breast maturation among girls who were already in stage II, when either the CA or the SA is increased by 1 year

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 11 to 12 years	− 1.8	from 11 to 12 years	+10.9
from 12 to 13 years	−14.7	from 12 to [illegible] years	+34.9
from 13 to 14 years	+14.4	from 13 to 14 years	+19.1
from 14 to 15 years	− 3.9	from 14 to 15 years	+14.9
Total	+6.2 ± 5.6	Total	+20.8 ± 6.0

when either CA or SA is increased by 1 year Since the difference was not clear the author studied also the alteration in the percentage attaining breast maturation stage IV among girls already in stage II when either the CA or the SA was increased by 1 year

The result is shown in Table 23 The difference between the average increase in percentage, 20 8 ± 6 0 and 6 2 ± 5 6 indicates a greater dependence upon SA than upon CA, even though the difference cannot be said to be significant ($u = 1.5$)

Conclusion

Thus, for breast maturation too there is a tendency for a greater dependence upon SA than upon CA.

Present Studies of the Development of Pubic Hair and Comparison with Previous Findings

Girls

Tables 24 and Fig 34 illustrate the *development of pubic hair in relation to chronological age* The almost parallel curves indicate the percentage of girls who had attained, at the various ages, stages II III and IV of pubic hair development.

In a few per cent pubic hair appears at the age of 9 /₂. Initially the curve ascends slowly then rather abruptly at the age of 11–12 years. At the age of 13 the growth of pubic hair was in progress in 90 %

Development of pubic hair from *stage II to stage IV* took place, on the average, from age $11^3/_4$ years to $13^1/_2$, i.e. in the course of about 2 years. In cases where pubic hair appeared late, i.e. after the age of 13 the development from stage II to IV took about 4 years.

The distribution curve illustrating

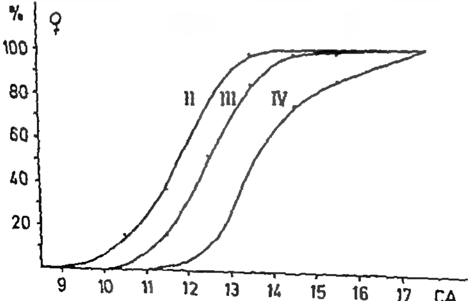

Fig 34

Percentage of girls who had reached stages II III and IV of pubic hair development in relation to chronological age (present material)

Table 24

Percentage of girl who had reached stages II III nd IV of pubic hair development n relation to SA and CA

Girls

SA years	Number	Stage II	4	Stage III	%	Stage IV	%	CA years	Number	Stage II	4	Stage III	%	Stage IV	%
6^{1} /	37	0	0	0	0	0	0	7–8	48	0	0	0	0	0	0
7^{10}/	55	0	0	0	0	0	0	8–9	40	0	0	0	0	0	0
$8^{10}/_{12}$	52	1	2	0	0	0	0	9–10	56	1	2	0	0	0	0
10	61	8	13	1	2	0	0	10–11	49	8	16	1	2	0	0
11	46	23	50	9	20	0	0	11–12	68	25	37	11	16	1	2
12	50	41	82	22	44	3	6	12–13	46	37	80	24	52	3	7
13	46	46	100	42	91	17	37	13–14	62	61	98	52	84	33	53
13 /	24	24	100	24	100	15	63								
14	26	26	100	26	100	24	92	14–15	55	55	100	54	98	41	75
15	40	40	100	39	100	36	90	15–16	51	51	100	50	98	44	86
16	40	40	100	40	100	34	85	16–17	30	30	100	30	100	26	87
17	31	31	100	31	100	31	100	17–18	21	21	100	21	100	21	100
18	15	15	100	15	100	15	100	18–18½	6	6	100	6	100	6	100

stage II of pubic hair development shows an almost normal distribution. According to the probit diagram the mean was 11.6 years and the standard deviation 1.0 year.

Table 25 presents the chronological ages at which the various stages of pubic hair appeared in this and other materials. Chapter 2 described the methods by which the development of pubic hair has been assessed.

To be able to compare the various results, the stages which, according to the description, correspond approximately to each other, are tabulated in the same columns, even though they have not always been given the same designation. Quaade's (1955) study and the present one carried out by the same method, show similar results.

In Hansman & Maresh material pubic hair appeared about 1 year earlier than in the present material, but this does not warrant any conclusions, as the details of Hansman & Maresh material are not given. The girls of Reynolds & Wines' material, which was unselected, also showed earlier maturation in respect to pubic hair, but the difference is only about 6 months. The stated standard deviations are in the same range as in the present series.

Just as for chronological age, the *development of pubic hair* plotted against *skeletal age* gives almost parallel curves illustrating the percentages of children who have reached stages II, III, and IV (Fig. 35) at different skeletal ages. However, the appearance of pubic hair, measured in skeletal age, occurs on the average at 11 years of age, i.e. somewhat earlier than found for the chronological age. The development of pubic hair from stage II to stage IV takes on the average a little more than 2 years. The distribution curve illustrating stage II is approximately normal. According to the probit diagram M was 11.0 years and the standard deviation 1.0 year.

Since the standard deviation for the time of appearance of pubic hair is 1.0 years, in terms of CA as well as of SA, no difference could be expected in the correlation between appearance of pubic hair and CA and between appearance of pubic hair and SA.

Hansman & Maresh found that the

Table 25

Chronological age at which the various stages of pubic hair development occur

Girls.

Author	Year of publication	Longitudinal cross-sectional study	No. of girls	Years of study	Stages		
Reynolds & Wines	1948	Longitudinal	49	1938–1946	II 11.0 ± 1.1	IV 12.5	V 13.9
Hansman & Maresh	1961	Longitudinal	36	unknown	II 10.7 ± 1.2		
Quaade	1955	Cross-sectional	509	1951	II 11 [illegible] – 12 [illegible]	III 12 [illegible] – 13 [illegible]	IV 12 [illegible] – 13 [illegible]
Present study		Cross-sectional	532	1964	II 11.6 ± 1.0	III 12.5	IV 13.4

The stages which, according to the description, correspond to each other are tabulated in the same column, even though they have not always been given the same designation.

Table 24

Percentage of girls who had reached stages II III and IV of pubic hair development in relation to SA and CA.

Girls.

SA years	Number	Stage II	%	Stage III	%	Stage IV	%	CA years	Number	Stage II	%	Stage III	%	Stage IV	%
6 /	37	0	0	0	0	0	0	7– 8	48	0	0	0	0	0	0
7 /	55	0	0	0	0	0	0	8– 9	40	0	0	0	0	0	0
8 /	52	1	2	0	0	0	0	9–10	56	1	2	0	0	0	0
10	61	8	13	1	2	0	0	10–11	49	8	16	1	2	0	0
11	40	23	50	9	20	0	0	11–12	68	25	37	11	16	1	2
12	50	41	82	22	44	3	6	12–13	46	37	80	24	52	3	7
13	46	46	100	42	91	17	37	13–14	62	61	98	52	84	33	53
13	24	24	100	24	100	15	63								
14	26	26	100	26	100	24	92	14–15	55	55	100	54	98	41	75
15	40	40	100	30	100	36	90	15–16	51	51	100	50	98	44	86
16	40	40	100	40	100	34	85	16–17	30	30	100	30	100	6	87
17	31	31	100	31	100	31	100	17–18	21	21	100	21	100	21	100
18	15	15	100	15	100	15	100	18–18½	6	6	100	6	100	6	100

stage II of pubic hair development shows an almost normal distribution. According to the probit diagram the mean was 11.6 years and the standard deviation 1.0 year.

Table 25 presents the chronological ages at which the various stages of pubic hair appeared in this and other materials. Chapter 2 described the methods by which the development of pubic hair has been assessed.

To be able to compare the various results, the stages which, according to the description, correspond approximately to each other are tabulated in the same columns, even though they have not always been given the same designation. Quaade's (1955) study and the present one carried out by the same method, show similar results.

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Since the standard deviation for the time of appearance of pubic hair is 1.0 years, in terms of CA as well as of SA, no difference could be expected in the correlation between appearance of pubic hair and CA and between appearance of pubic hair and SA.

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Reynolds & Wines	1948	Longitudinal	49	1938–1946	II 11.0 ± 1.1	IV 12.5	V 13.9
Hansman & Maresh	1961	Longitudinal	36	unknown	II 10.7 ± 1.2		
Quaade	1955	Cross-sectional	509	1951	II $11\,{}^{1}/_{12}-12^{9}/_{12}$	III $12^{9}/_{12}-13^{9}/_{12}$	IV $12^{10}/_{12}-13^{9}/$
Present study		Cross-sectional	552	1964	II 11.6 ± 1.0	III 12.5	IV 13.4

The stages which, according to the description, correspond to each other are tabulated in the same columns, even though they have not always been given the same designation.

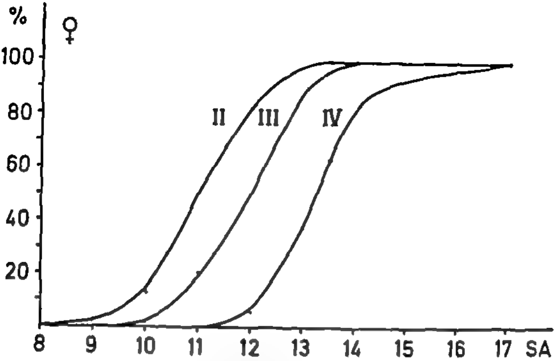


Fig 35

Percentage of girls who had attained stages II III and IV of pubic hair development in relation to skeletal age (present material)

age at appearance of pubic hair had a SD *of* 1 2 *years for* CA *and of* 1 1 years for SA. Pubic hair development was not studied in the Brush Foundation material.

In order to judge more closely the correlations between pubic hair development and chronological age as well as between pubic hair development and skeletal age, the author analysed how the percentage of girls who had attained stage II varied when CA was constant and SA increased by 1 year and *vice versa*. The difference was

Table 26

Change in the percentage who attained stage IV of pubic hair development among girls who were already in stage II when either the CA or the SA increased by 1 year

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	*SA increased*	Difference in %
from 11 to 12 years	− 4 44	from 11 to 12 years	+ 6 13
from 12 to 13 years	+26.20	from 12 to 13 years	+22.59
from 13 to 14 years	+ 1 99	from 13 to 14 years	+49.92
from 14 to 15 years	− 8.54	from 14 to 15 years	− 0.56
from 15 to 16 years	−21 20	from 15 to 16 years	− 3 89
from 16 to 17 years	+10.94	from 16 to 17 years	+21 19
Total	+1 35 ± 5 1	Total	+16.28 ± 5.3

Tabl 27

Percentage of boy ho had tta ned stages II III and IV of pubic hair development i relation to SA nd CA.

Boys.

SA years	Number	Stage II	%	Stage III	%	Stage IV	%
5	4	0	0	0	0	0	0
6	5	0	0	0	0	0	0
7	11	0	0	0	0	0	0
8	37	0	0	0	0	0	0
9	43	0	0	0	0	0	0
10	41	0	0	0	0	0	0
11	37	2	3	1	3	0	0
11 ½	35	0	17	0	0	0	0
12 ½	41	18	41	3	7	0	0
13	25	18	78	7	30	0	0
13 ½	42	19	91	10	40	1	3
14	31	33	98	43	83	30	56
15	17	17	100	17	100	15	88
15 ½	10	10	100	10	100	10	100
16	9	9	100	9	100	9	100
17	21	21	100	1	100	21	100
18	13	13	100	13	100	13	100
19	6	6	100	6	100	6	100

CA years	Number	Stage II	%	Stage III	%	Stage IV	%
7–8	48	0	0	0	0	0	0
8–9	43	0	0	0	0	0	0
9–10	57	0	0	0	0	0	0
10–11	48	1	2	0	0	0	0
11–12	48	4	8	0	0	0	0
12–13	39	1	31	0	0	0	0
13–14	32	39	75	21	40	10	19
14–15	56	31	93	39	70	23	11
15–16	33	31	94	27	8[illegible]	22	67
16–17	27	15	100	46	96	21	78
17–18	15	15	100	15	100	15	100
18–18 ½	11	11	100	11	100	11	100

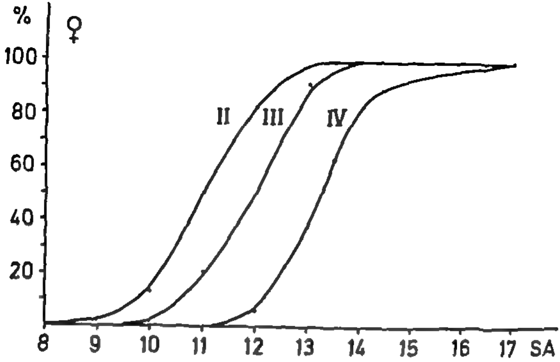


Fig 35

Percentage of girls who had attained stages II III and IV of pubic hair development in relation to skeletal age (present material)

age at appearance of pubic hair had a SD of 1 2 years for CA and of 1 1 years for SA. Public hair development was not studied in the Brush Foundation material

In order to judge more closely the correlations between pubic hair development and chronological age as well as between pubic hair development and skeletal age, the author analysed how the percentage of girls who had attained stage II varied when CA was constant and SA increased by 1 year and *vice versa*. The difference was

Table 26

Change in the percentage who attained stage IV of pubic hair development among girls who were already in stage II when either the CA or the SA is increased by 1 year

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 11 to 12 years	− 4 44	from 11 to 1 years	+ 6.13
from 12 to 13 years	+26.20	from 12 to 13 years	+22.59
from 13 to 14 years	+ 1.99	from 13 to 14 y ars	+49.9?
from 14 to 15 years	− 8.54	from 14 to 15 years	− 0.36
from 15 to 16 years	−21.20	from 15 to 16 years	− 3.89
from 16 to 17 years	+10.94	from 16 to 17 years	+21 19
Total	+1.35 ± 3 1	Total	+16.28 ± 5.3

Table 27

Percentage of boys who had attained stages II, III, and IV of pubic hair development in relation to SA and CA.

Boys

SA years	Number	Stage II	%	Stage III	%	Stage IV	%
5	4	0	0	0	0	0	0
6	23	0	0	0	0	0	0
7	41	0	0	0	0	0	0
8	37	0	0	0	0	0	0
9	45	0	0	0	0	0	0
10	41	0	0	0	0	0	0
11	37	2	5	1	3	0	0
11½	35	6	1	0	0	0	0
12½	41	18	44	3	7	0	0
13	23	18	78	7	30	0	0
13½	22	19	91	10	46	1	5
14	34	33	98	45	83	30	56
15	17	17	100	17	100	15	88
15½	10	10	100	10	100	10	100
16	9	9	100	9	100	9	100
17	21	21	100	21	100	21	100
18	13	13	100	13	100	13	100
19	6	6	100	6	100	6	100

CA years	Number	Stage II	%	Stage III	%	Stage IV	%
7–8	48	0	0	0	0	0	0
8–9	43	0	0	0	0	0	0
9–10	37	0	0	0	0	0	0
10–11	48	1	2	0	0	0	0
11–12	48	4	8	0	0	0	0
12–13	39	12	31	0	0	0	0
13–14	52	39	75	1	40	10	19
14–15	56	51	93	39	70	23	41
15–16	33	31	94	27	82	22	67
16–17	27	15	100	26	[illegible]	21	78
17–18	15	15	100	15	100	15	100
18–18½	11	11	100	11	100	11	100

not significant. Thereafter the author investigated the increase in the percent age who attained pubic hair stage IV among girls who had already reached stage II when the CA and the SA respectively was increased by 1 year

The result is presented in Table 26 The significant difference between the average increase in the percentage + 1.35 when the SA is held constant and the CA is increased and + 16 28 when the CA is held constant and the SA is increased indicates a *closer correlation between pubic hair development and SA than between pubic hair development and CA* (u = 2 0*)

Boys

The development of pubic hair in relation to chronological age is illustrated in Table 27 and Fig 36

The 3 curves represent the percent age of boys who attain at the various ages, stages *II III* and *IV* of pubic hair development. The curves are very similar to those shown above for the girls.

In a very few per cent pubic hair starts appearing at the age of 10½. Initially the curve (stage II) ascends slowly thereafter rather abruptly around the age of 13 At the age of 14 the development of pubic hair is in progress in about 90 %

The development of pubic hair from stage II to IV takes place, on the average from age 12 8 to 15 2 years, i.e. in the course of a little more than 2 years.

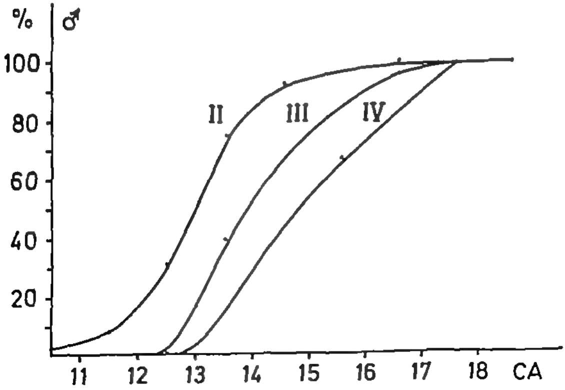


Fig 36

Percentage of boys who had attained stages II III and IV of pubic hair development in relation to chronological age (present material)

Table 28

Chronological age at which the various stages of pubic hair development occur

Boys.

Author	Year of publication	Longitudinal/cross-sectional study	No. of boys	Years of study	Stages		
Reynolds & Wines	1951	Longitudinal	59	1933–1946	II 12.2±1.1	IV 13.9	V 16.1
Hansman & Maresh	1961	Longitudinal	27	unknown	II 12.8±1.1		
Quaade	1955	Cross-sectional	489	1951	II $1^{00}/_{12}-13^{9}/_{12}$	III $13\ /_{12}-14^{2}/_{12}$	IV $14\ /_{12}-15^{2}/_{12}$
Present study		Cross-sectional	477	1964	II 12.8±1.1	III 13.8	IV 15.2

The stages which, according to the description, correspond to each other are tabulated in the same column, even though they have not always been given the same designation.

The distribution curve showing pubic hair stage II is approximately normal. According to the probit diagram, the mean was 12.8 years and the standard deviation 1.1 years. Thus, the mean is 1.2 years later than for the girls. Table 28 gives the ages at appearance of pubic hair in the studies of previous authors.

These ages at appearance of pubic

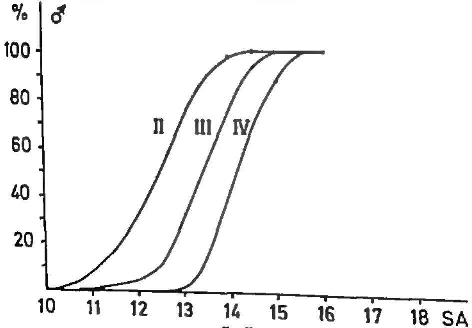


Fig. 37

Percentage of boys who had attained stages II, III, and IV of pubic hair development in relation to skeletal age (present material)

hair show fairly good conformity in the various studies.

Plotting the development of pubic hair against skeletal age again gives 3 almost parallel curves, representing *pubic hair in stages II III and IV* (Fig 37) The points on the stage II curve give, when inserted in a probit diagram, an almost rectilinear course, i e. an approximately normal distribution in which the mean was 12.4 years and the standard deviation 0 9 year Thus the mean with constant skeletal age is 0 4 year lower than with constant chronological age. This is presumably because the present children were retarded in relation to the children of the American material.

Since the difference between the standard deviation 1 1 years with constant chronological age and 0.9 year with constant skeletal age is not great no difference can be expected in the dependence of pubic hair upon CA and upon SA respectively

Hansman & Maresh found that the age of appearance of pubic hair had a standard deviation of 1 1 years for CA and of 0 8 year for SA.

In order to judge more closely the correlations between pubic hair development and chronological age as well as between pubic hair development and skeletal age, the author investigated as for the girls, the change in the percentage of boys who attained pubic hair stage IV among the boys who were already in stage II when the CA and the SA respectively was increased by 1 year

The result is shown in Table 29 The difference between the increased percentage, 5 0 when SA is held constant and the chronological age is increased and + 34 7 when CA is held constant and SA increased shows a *significantly higher correlation between pubic hair development and SA than between pubic hair development and CA* (u = 4 0***)

Table 29

Change in the percentage who attained stage IV of pubic hai development among boys who were already in stage II when either the CA or the SA is ncreased by 1 year

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 12 to 13 years	+10 6	from 12 to 13 years	+ 3.9
from 13 to 14 years	− 5 1	from 13 to 14 years	+38 4
from 14 to 15 years	− 3 6	from 14 to 15 years	+32.2
from 15 t 16 years	−17 9	from 15 to 16 years	+22.3
Total	− 5 0 ± 6.8	Total	+34 7 ± 7.2

Chapter 11

Studies of Testes Development

Previous Studies

Scammon (1930) in an autopsy study determined the weight of the testicles from 726 boys aged 0–20. He found the weight to be fairly constant up to the age of 11 whereupon it rose steeply up to age 20.

Only a few *in vivo* measurements have been reported. Reich (1924) measured the length and smallest width in 221 boys aged 0–15 years. The size

Table 30

Polar sum of testes (mm) in relation to chronological age in previous and present studies.

CA [illegible]	[illegible] & [illegible]	Average [illegible] Quetelet [illegible]	Average [illegible] Present study
7		18	
7 6/12		18	17
8		18	
8 6/12		17	16
9		17	
9 6/12		19	18
10		19	
10 6/12		19	19
11		20	
11 6/12		21	23
12	17	21	
12 6/12		26	28
13	20	26	
13 6/12		34	34
14	28	35	
14 6/12		36	38
15	33	40	
15 6/12			42
16	39		
16 6/12			43
17	41		
17 6/12			43
18			
18 6/12			
19	43		

was found to be approximately unchanged up to 11 years of age, while from 11–16 the testes grew by 17–35 mm.

From-Hansen & With (1951) measured the testes of 251 boys under 20 years of age. The minimum values are shown in Table 30 which gives also the values found by Quaade (1955) in a study of 473 boys aged 7–15. In this latter material there was a considerable standard deviation within each age group. Means and standard deviations were unchanged up to 11–12 years, whereupon the means increased abruptly and the standard deviations too showed an appreciable increase.

Present Studies

Testicular size in relation to CA and SA is given in Table 31. The curve (Fig. 38) representing the *polar measurements of the testes in relation to chronological age* runs an almost horizontal course up to the age of 7–9 years. At 10 years *it starts ascending a little, from 11–14 years the rise is quite* abrupt, and then *the curve flattens* again. From 9–18 years of age the polar measurements of the testes increase by an average of 17–43 mm. The velocity curve (Fig. 39) shows that the peak increment occurs at the age 12 ½–13 years.

When the *testes measurements are*

Table 31

Testes size in relation to chronological age and skeletal age.

CA years	N	Polar meas. mm	SA years	No.	Polar meas. mm
7 – 7½	18	17	7	40	17
7½– 8	30	17			
8 – 8½	26	17	8	37	17
8½– 9	17	16			
9 – 9½	25	18	9	42	18
9½–10	32	[illegible]			
10 –10½	28	19	10	41	20
10½–11	20	19			
11 –11½	24	22	11	37	22
11½–12	24	25	11½	35	25
12 –12½	20	26			
12½–13	19	29	12½	41	30
13 –13½	28	32	13	5	31
13½–14	24	35	13	22	36
14 –14½	30	34	14	34	40
14½–15	26	40			
15 –15	19	42	15	13	4
15½–16	14	42	15½	1	44
16 –16½	13	43	16	9	44
16½–17	14	44			
17 –17½	8	45	17	21	43
17½–18	7	41			
18 –18	11	45	18	13	43
			19	[illegible]	44

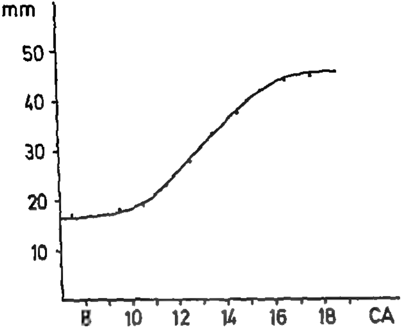


Fig 38

Polar size of testes in relation to chronological age (present material)

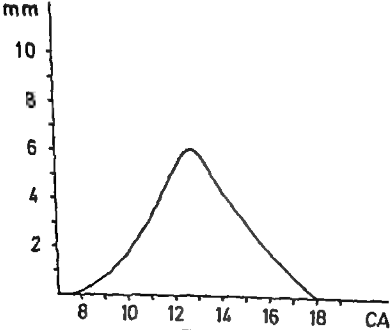


Fig 39

Velocity curve of testes growth in relation to chronological age (present material)

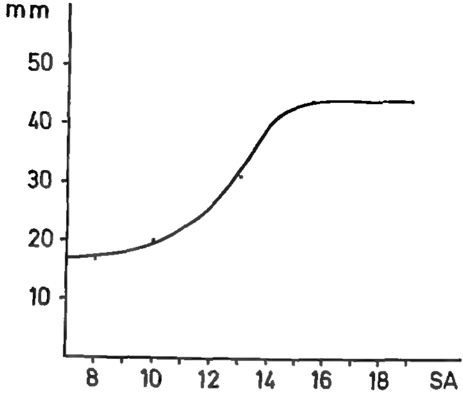


Fig 40

Polar size of testes in relation to skeletal age (present material)

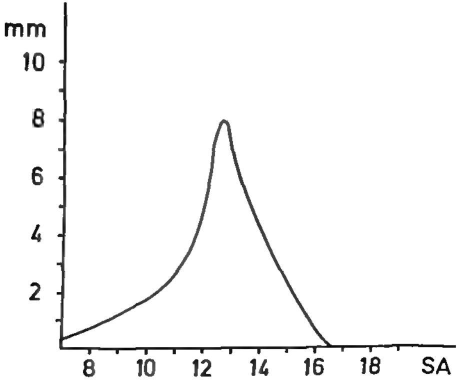


Fig 41

Velocity curve of testes growth in relation to skel tal age (present material)

Table 32.

Change in polar size of testes (mm) when SA or CA is increased by 1 year

Increase in age	Change in testicular size when CA is increased by 1 year and SA held constant		Change in testicular size when SA is increased by 1 year and CA held constant	
from 8 to 9 years	+1.0		+0.1	
from 9 to 10 years	+0.4	+0.7 ± 0.2	+1.0	+0.0 ± 0.5
from 10 to 11 years	+2.7		−1.4	
from 11 to 12 years	+2.3		+3.2	
from 12 to 13 years	+4.7	+2.2 ± 0.8	−0.1	+4.6 ± 0.8
from 13 to 14 years	+0.3		+7.6	
from 14 to 15 years	+3.3		+1.7	
from 15 to 16 years	−0.2		+4.5	
from 16 to 17 years	−0.7	+1.7 ± 0.9	+1.5	+1.4 ± 0.9
from 17 to 18 years	+3.2		−0.9	
	Total	+1.7 ± 0.5	Total	+1.9 ± 0.5

plotted against skeletal age it appears, in particular from the velocity curve (Fig 41) that the peak increment is greater than in Fig 39

From Fig 38 it was apparent that the testes increase in size by 25–40 mm in the course of 3 chronological years, while the same increment occurs in 2 ½ years when measured in skeletal years (Fig 40) This finding that the greater part of the increment measured in skeletal years, occurs within a shorter period than when measured in chronological years, gives rise to the presumption that testicular development is more closely related to SA than to CA.

To assess in more detail the relation between testicular growth and CA and between testicular growth and SA, the author studied the average increment when SA was held constant and CA increased by 1 year and *vice versa*. The result is presented in Table 32 which shows the average gain during 3 periods corresponding to the above mentioned age periods (1) the pre adolescent period during which the testes grow very slowly (2) the period *from 11–14 years during* which the greatest increment takes place, and (3) the period during which the growth rate decreases considerably

Conclusion

On the whole, it was not possible to *demonstrate* a significant difference in testes increment when the SA and CA respectively was increased, but in the intermediate age group, from 11–14 years of age, when the greatest increment occurs, there is a *significantly* greater increment when SA than when CA is increased by 1 year viz. 4 6 mm as compared with 2.2 mm (u = 2.1)

Chapter 12

Studies of Penis Development

Table 33 shows, for Quaade's (1955) and the present material the variation in penis length with age. The results of the two studies are very similar

Table 34 and Fig 42 give, for the present material, the *average length of the penis at the different chronological ages* Up to the age of 12 years the penis grows but slowly from 12–15 years rapidly and thereafter the growth rate gradually slows down.

Fig 43 illustrates the *relation between penis length and skeletal age* This curve is of approximately the same shape as that in Fig 42 but steeper during the period of maximum growth It is apparent, particularly from the velocity curves in Figs. 44 and 45 that the peak increment is greater when measured in SA than in CA. This might indicate a greater correlation between penile growth and SA than between penile growth and CA.

To assess more closely the relation between penile growth and CA as well as between penile growth and SA the author studied the average increment when SA was held constant and CA increased by 1 year and *vice versa*

The result is apparent from Table 35 Just as for the testes, the average increment during 3 periods was calculated (1) the pre-adolescent period during which the penis grows very slowly (2) the period from 12–15 years during which the greatest increment occurs, and (3) the period during which the growth rate decreases considerably

Table 33

Penis size in Quaade's and the present material.

CA years	Quaade material mm	Present material mm
7	50	
7 1/2	50	39
8	47	
8 1/2	47	40
9	50	
9 1/2	50	42
10	46	
10 1/2	50	42
11	51	
11 1/2	49	43
12	50	
12 1/2	51	46
13	55	
13 1/2	67	60
14	57	
14 1/2	70	69
15	87	
15 1/2		76
16		
16 1/2		80
17		
17 1/2		84
18		
18 1/2		84

Table 34

Penis size in relation to skeletal age and chronological age.

CA years	Number	mm	SA years	Number	mm
7	40	39	7– 8	38	39
8	37	38	8– 9	43	40
9	42	43	9–10	37	42
10	41	42	10–11	48	4
11	37	45	11 12	48	43
11½	35	45	12 13	39	46
12½	41	49			
13	23	52	13–14	52	60
13½	[illegible]	67			
14	54	72	14–15	56	69
15	[illegible]	75	15–16	33	76
15½	12	74			
16	9	79	16–17	27	80
17	21	84	17–18	15	[illegible]
18	[illegible]	85	18–18 /	11	[illegible]
[illegible]	6	81			

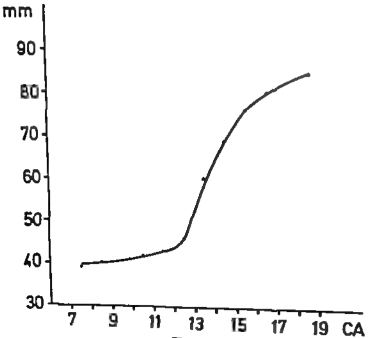


Fig 42

Penis size in relation to chronological age (present material)

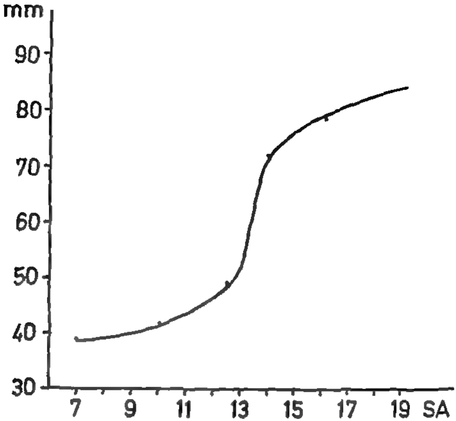
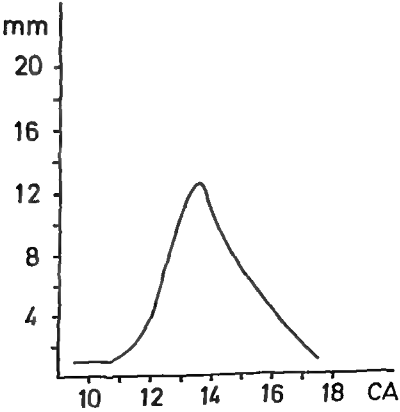


Fig 43
Penis size in relation to skeletal age (present material)



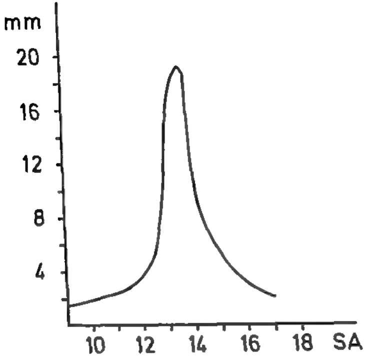


Fig 45

Velocity curve of penis growth in relation to skeletal age (present material)

Table 33

Change in penis size (mm) when SA or CA is increased by 1 year

Increase in age	Change in penis size when CA is increased by 1 year and SA is held constant		Change in penis size when SA is increased by 1 year and CA is held constant	
from 7 to 8 years	+2.0		−1.4	
from 8 to 9 years	+2.1		+4.7	
from 9 to 10 years	−1.5	+0.6 ± 0.6	−1.8	0.3 ± 0.6
from 10 to 11 years	+0.4		−0.1	
from 11 to 12 years	+0.2		+1.3	
from 12 to 13 years	+8.3		+6.9	
from [illegible] to 14 years	+2.6	+3.7 ± 1.6	+11.2	+7.5 ± 1.8
from 14 to 15 years	+0.6		+3.5	
from 15 to 16 years	+0.4		+0.2	
from 16 to 17 years	+2.8	2.3 ± 3.3	+5.6	1.7 ± 3.1
from 17 to 18 years	+[illegible].2		+5.5	
	Total	1.8 ± 0.8	Total	3.1 ± 0.9

Conclusion

On the whole, it was not possible to demonstrate any difference in penis growth when the SA and CA respectively was increased. Within the intermediate age period 12–15 years, when the maximum growth takes place there is a tendency to a greater increment when the SA than when the CA is increased by 1 year 7.5 and 3.7 mm respectively, but this difference is not significant (u = 1.6)

Chapter 13

Studies of the Age of Voice Change and Appearance of Moustache

Change of Voice

The relationship between the change of voice and CA on the one hand and SA on the other as found in the present material is shown in Table 36 and in Figs. 46 and 47. In 50 % of the boys the voice had broken at chronological age 15 1/2 and at skeletal age 15 years. This difference of 6 months is presumably due to the fact that skeletally the present children were retarded by 6 months in relation to the Brush Foundation material.

In Quaade's (1955) material the voice had broken at an average age of 15 years. According to Tanner the change of voice takes place at the time that the penis is about to complete its development. This occurred in the present material at 15–16 years of age.

The curve in Fig. 47 is steeper than that in Fig. 46 indicating perhaps a

Table 36

Change of voice in relation to skeletal age and chronological age.

SA years	Number	Number whose voice had broken	%	CA years	Number	Number whose voice had broken	%
5	4	0	0				
[illegible]	23	0	0				
[illegible]	41	0	0	7–8	48	0	[illegible]
8	37	0	0	8–9	43	0	0
9	43	0	0	9–10	57	0	0
10	41	0	0	10–11	48	0	0
11	37	1	3	11–12	48	0	0
11	25	0	0				
12 1/2	41	0	0	12–13	39	0	0
13	23	0	0	13–14	52	5	10
13 1/2	22	1	5				
14	[illegible]	16	29	14–15	56	12	21
15	17	7	41	15–16	33	19	58
15 1/2	10	9	90				
16	9	6	66	16–17	27	19	70
17	21	20	95	17–18	15	13	87
18	15	15	100	18–18 1/2	11	11	100
19	6	6	100				

Conclusion

On the whole, it was not possible to demonstrate any difference in penis growth when the SA and CA respectively was increased. Within the intermediate age period 12–15 years, when the maximum growth takes place, there is a tendency to a greater increment when the SA than when the CA is increased by 1 year 7.5 and 3.7 mm respectively but this difference is not significant ($u = 1.6$)

Table 37

Change in percentage of boys whose voice had broken when either skeletal age or chronological age is increased by 1 year. Chronological age means whole, completed years.

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 12 to 13 years	+2.8	from 12 to [illegible] years	+3 0
from 13 to 14 years	+4.5	from 13 to 14 years	+17 4
from 14 to 15 years	+9.2	from 14 to 15 years	+31.8
from 15 to 16 years	−17.6	from 15 to 16 years	+9 8
from 16 to 17 years	−27.1	from 16 to 17 years	+18.1
Total	−1.3 ± 6.5	Total	+23.6 ± 6.3

higher correlation between change of voice and SA than between change of voice and CA. To study this aspect in more detail, the author investigated the variation in the percentage of boys whose voice had broken when the CA was held constant and the SA increased by 1 year and *vice versa*. The results are given in Table 37 which shows a distinctly significant difference between the average increase in percentage + 23 6 ± 6.3 when the SA is increased and the CA held constant and − 1.3 ± 6.5 when the CA is increased and the SA held constant (u = 2.7**)

Appearance of Moustache

The age of appearance of moustache, measured in CA and SA, is shown in

Table 38

Appearance of moustache in relation to skeletal age and chronological age.

SA years	Number	Number of boys with moustache	%	CA years	Number	Number of boys with moustache	%
5	4	0	[illegible]				
6	23	0	[illegible]				
7	41	0	0	7– 8	48	0	0
8	37	0	0	8– 9	43	0	0
9	43	0	0	9–10	37	0	0
10	41	0	0	10–11	48	0	0
11	37	0	0	11–12	48	0	0
11 /	33	2	6				
$12\,^{2}/_{3}$	41	3	7	12 13	39	1	3
13	23	5	22	13–14	[illegible]	13	25
$13\,^{1}/_{3}$	22	4	18				
14	54	38	68	14–15	56	33	[illegible]
15	17	16	94	15–16	33	27	82
$15\,^{2}/$	10	10	100				
16	9	9	100	16–17	27	26	96
17	21	21	100	17–18	15	15	100
18	13	[illegible]	100	$18–18\,^{1}/_{2}$	11	11	100
19	6	6	100				

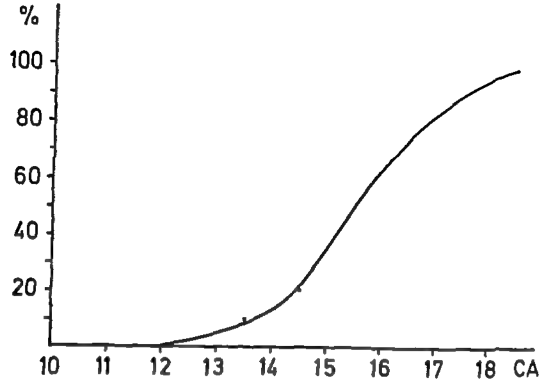


Fig 46
Percentage of boys whose voice had broken in relation to chronological age (present material)

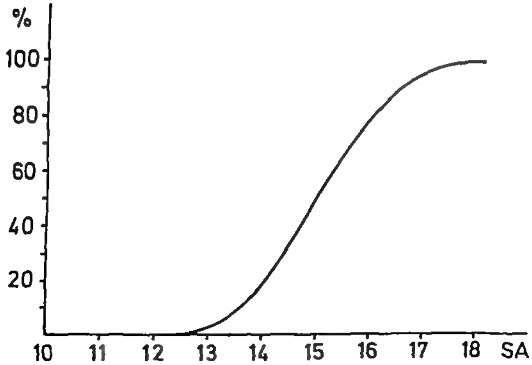


Fig 47
Percentage of boys whose voice had broken in relation to skeletal age (present material)

Table 37

Change in percentage of boys whose voice had broken when either skeletal age or chronological age is increased by 1 year. Chronological age means whole, completed years

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from 12 to 13 years	+2.8	from 12 to 13 years	+3.0
from 13 to 14 years	+4.3	from 13 to 14 years	+17.4
from 14 to 15 years	+9.2	from 14 to 15 years	+31.8
from [illegible] to [illegible] years	−17.6	from 15 to 16 years	+9.8
from 16 to 17 years	− 7.1	from 16 to 17 years	+18.1
Total	−1.3 ± 6.5	Total	+23.6 ± 6.3

higher correlation between change of voice and SA than between change of voice and CA. To study this aspect in more detail, the author investigated the variation in the percentage of boys whose voice had broken when the CA was held constant and the SA increased by 1 year and *vice versa.* The results are given in Table 37 which shows a distinctly significant difference between the average increase in percentage + 23.6 ± 6.3 when the SA is increased and the CA held constant and − 1.3 ± 6.5 when the CA is increased and the SA held constant (u = 2.7**)

Appearance of Moustache

The age of appearance of moustache, measured in CA and SA, is shown in

Table 38.

Appearance of moustache in relation to skeletal age and chronological age.

SA years	Number	Number of boys with moustache	%
5	4	0	0
6	23	0	0
7	41	0	0
8	37	0	0
9	43	0	0
10	41	0	0
11	37	0	0
11½	33	2	6
12½	41	3	7
13	23	5	22
13½	22	4	18
14	54	38	68
15	17	16	94
15½	10	10	100
16	9	9	100
17	21	21	100
18	13	13	100
19	6	6	100

CA years	Number	Number of boys with moustache	%
7–8	48	0	0
8–9	43	0	0
9–10	57	0	0
10–11	48	0	0
11–12	48	0	[illegible]
12–[illegible]	39	1	3
13–14	52	[illegible]	25
14–15	56	[illegible]	63
15–16	33	27	82
16–17	27	26	96
17–18	15	15	100
18–18½	11	11	100

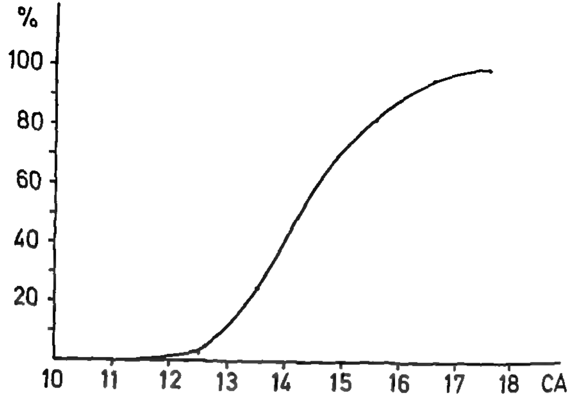


Fig 48
Percentage of boys with moustache in relation to chronological age (present material)

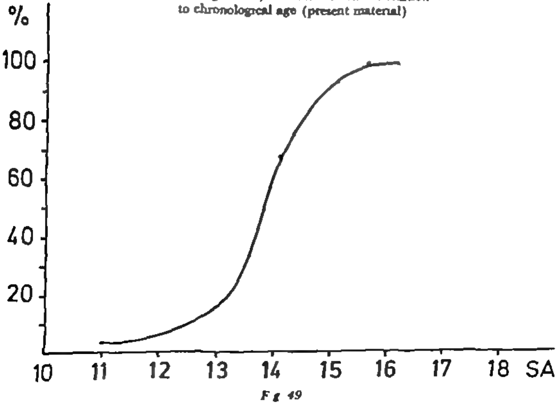


Fig 49
Percentage of boys with moustache in relation to skeletal age (present material)

Table 39

Change in percentage of boys with moustache when either the skeletal age or the chronological age is increased by 1 year
Chronological age means whole, completed years.

Skeletal age held constant		Chronological age held constant	
CA increased	Difference in %	SA increased	Difference in %
from [illegible] to 13 years	+8.4	from 12 to 13 years	+3.5
from 13 to 14 years	+17 4	from 13 to 14 years	+43 0
from 14 to 15 years	−3 9	from 14 to 15 years	+20.8
from 15 to 16 years	+5.6	from [illegible] to 16 years	−1 4
from 16 to 17 years	−27.2	from 16 to 17 years	+12.6
Total	+3.8 ± 6 5	Total	+20.7 ± 6 4

Table 38 and in Figs. 48 and 49 A moustache had appeared in 50 % at chronological age 14 /4 years and at skeletal age approx. 13³/ years.

The time of appearance of moustache in Quaade s (1955) material was about 15 years.

The curve illustrating the relationship between the appearance of a moustache and skeletal age is steeper than the curve plotting the appearance of moustache against chronological age. This indicates *a higher correlation between growth of beard and skeletal age than between growth of beard and chronological age*

The average increase in the percentage of boys who had acquired a moustache when the SA and CA respectively was increased by 1 year is shown in Table 39 There is a marked tendency to a higher correlation between SA and the appearance of a moustache than between CA and the appearance of a moustache, but the difference is not significant (u = 1 9)

Chapter 14

Skeletal Maturation and Social Conditions

It is generally assumed that the growth and development of children is determined by genetic as well as environmental factors.

The important role of *heredity* in growth and development has been demonstrated int al by Reynolds & Schoen in longitudinal studies of monozygotic triplets aged 8–18 years.

Their studies clearly showed the extremely uniform maturational patterns, there being no differences in height increment, skeletal maturation time of appearance of secondary sex characters, or time of eruption of teeth.

Hormonal production in the endocrine glands, governed by genetic as well as external factors, plays a decisive role in normal growth and development. This is known from endocrinology, in particular paediatric endocrinology as abnormalities in hormone production and in the mutual interaction of the hormones cause primarily disturbances of growth and development.

External factors which may affect growth are nutrition general hygiene including housing and diseases.

A comprehensive literature has accumulated on studies aiming at elucidating the influence of conditions of living upon height gain but only a few have been concerned with the influence of living conditions upon skeletal maturation The most important of these studies will be reviewed below

Todd found that the *social conditions* of children *influence their skeletal maturation* By selecting for the Brush Foundation study children from the best social circumstances who had always been in good health, he tried as far as possible to reduce the variations in skeletal maturation which is caused by differences in external factors.

Greulich (1951) studied the height weight and skeletal maturity of 1800 school children aged 6–17 years in the isle of Guam which was occupied by Japanese forces during World War II Conditions of living especially in respect to nutrition, were rather poor at that time. Skeletal age was assessed by the Greulich & Pyle atlas method Both boys and girls proved to be skeletally retarded as compared with the Brush Foundation children the boys by an average of 21 months and the girls by an average of 14 months They were retarded also in height and weight, the boys more so than the girls.

This phenomenon viz. that male *individuals are more susceptible than*

females to unfavourable external conditions, is known from the higher perinatal mortality among boys than among girls.

Stuart (cited by Greulich & Pyle 1959) studying the skeletal age of children in Boston, 50–60 from each group, found the boys to be retarded by an average of 2 months in relation to the Brush Foundation material. The mean standard deviation was 12.0 months. The girls were retarded by an average of 3 months. The mean SA was 11.3 months.

Sutow in 1952, set up standards of the skeletal maturation of the hand on the basis of 2370 healthy Japanese children aged 6–19 years. Assessing his standards by the Greulich & Pyle atlas method he found the Japanese girls to be retarded by an average of 17 months as compared with the American girls of the Brush Foundation study and the boys by an average of 14 months.

Greulich (1951) felt that this retardation was due rather to poor conditions of living than to racial differences.

This assumption is supported by a study performed by Greulich in 1956–1957 on 898 children born in America, but of Japanese parents. Their height, weight, and skeletal age were compared with the findings of Sutow in Japanese children in Japan 1952. The Japanese children born in U.S.A. were significantly taller heavier and skeletally more advanced than the Japanese children born in Japan. Comparison of the SA in the American-born Japanese children with the SA in the children of the Brush Foundation study showed the Japanese boys aged 5–7 years to be significantly retarded in skeletal age, average 7.0 months. At 13–17 years of age they were significantly advanced, average 8.5 months. At intermediate ages there was no significant difference. The Japanese girls born in U.S.A. were significantly advanced in relation to the American Brush Foundation children in the age range 10–17 years, average 10.0 months, but at other ages there was no significant difference.

These findings, in particular the similarity in skeletal maturity between American-born Japanese and the Brush Foundation children, should urge to caution in explaining a retarded growth in children from the less favoured parts of the world by racial differences.

Dreizen et al. (1957 b) studied the *importance of nutrition to the maturation of the hand skeleton* by investigating skeletal maturation in children exhibiting clinical signs of severe nutritional disturbances, such as pellagra dermatitis, beriberi neuritis, cheilosis, ocular signs in riboflavin deficiency and scurvy.

In 54 boys and 64 girls he found an average skeletal retardation of 13.5 and 12.0 months respectively while in a healthy control group of 53 boys and 80 girls he found a retardation of 0.5 and 0.6 months. This material was derived from the Nutrition Clinic, Hillmann Hospital, Birmingham, Alabama.

In 1954 Dreizen et al. had demonstrated the importance of nutrition to skeletal maturation in 160 children with clinical signs of nutritional dis-

Chapter 14

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External factors which may affect growth are nutrition, general hygiene including housing and diseases.

A comprehensive literature has accumulated on studies aiming at elucidating the influence of conditions of living upon height gain but only a few have been concerned with the influence of living conditions upon skeletal maturation. The most important of these studies will be reviewed below

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This phenomenon, viz. that male individuals are more susceptible than

a significant positive correlation between the height of parents and children, independent of the income, and a significant—though smaller—positive correlation between children's height and their parents' income, when the parents' height was held constant.

In England Hammond's (1953) study on the height of 2925 children from private schools and council schools in slum districts showed that the children from private schools were 1–3 height years taller than the children from slums.

Berry & Cowin (1954) measuring the height of 14 year-old boys in private schools and in council schools found an average height of 166.5 ± 6.8 cm and 158.3 ± 8.9 cm respectively.

The increase in adult height which has taken place is due predominantly to improved social circumstances. This has been demonstrated by Acheson & Fowler (1964) in a study of the difference in height between two generations in a part of London where the standard of living had not changed appreciably as well as in a mining village in Wales where the standard of living had improved considerably in the course of the past 20 years. The difference between parents' height and the children's adult height (predicted on the basis of skeletal age assessment by Greulich & Pyle's atlas and Bayley Pinneau's height tables) was greater in Wales than in London.

The influence of social factors upon the time of the menarche has also been studied—in Norway by Schiøtz in 1928. He found the menarche in 2,008 girls from the higher social strata to have occurred an average of 3 months earlier than in 7 161 girls from socially lower classes in Oslo.

Bojlén et al. could just demonstrate a significant difference in the time of menarche, when grouping the girls by father's occupation the menarche occurring earlier in the socially better off groups.

Influence of Disease Upon Skeletal Maturation

From the papers of Dreizen et al. (1954) it is apparent that nutritional defects which are so severe as to cause clinical signs also cause retardation of skeletal maturation.

Meredith & Knott (1962) made semi-annual measurements of the height of 66 boys from the age of 5 to 10 years and of 73 girls from the age of 5 to 9 years. All these children were of higher social classes. The 20 % who had a history of least illness, mainly children's diseases, and colds and the 20 % who had a history of most illness, e. g. asthma, mild polio otitis, sinusitis, bronchitis, or acute nephritis in the course of the study period, were picked out and their height increment compared. The children of the group with most illness did not show a slower growth than the healthiest children.

In 87 children with congenital isolated ventricular septal defect Sandoe (1963) found no definite influence upon height.

Summing up, these investigations have shown a connection between less favourable social circumstances and retarded skeletal maturation—less fa-

turbances. All the children showed retarded skeletal maturity. All 28 ossification centres in the hand and wrist were retarded, but in different degrees. 82 of these children were given for 6 months 2 litres of milk in addition to their usual diet. Repeated determination of skeletal age showed that during these 6 months growth had been 1.7 times faster than normal. Those centres which according to the child's age were expected to grow fastest gave the best response to the treatment.

Prader, Tanner & van Harnack (1963) have called this phenomenon —viz. that after a period of retarded growth because of illness or starvation children show a tendency to make up for the loss and to follow their own previous growth curve—the catch up phenomenon.

Achesen & Hewitt (1954) in a longitudinal study of boys and girls aged 1 ¹/₂–5 years, made 2828 assessments of height and skeletal age and grouped the children into two social classes according to their father's occupation. They found the children of the socially higher class to be advanced in relation to children from the socially lower class, in respect to skeletal development as well as height. There was less difference between the girls than between the boys of the two classes. No attempt is made to explain this fact, but it is in keeping with Greulich's (1951) finding that boys are more vulnerable than girls to unfavourable external circumstances.

In Scandinavia the *influence of social factors upon height* has been investigated by Key in 1891. Measuring the height of 18 000 boys and girls in Stockholm from private as well as from council schools, he found the children from the council schools to be smaller than those from the private schools. The difference was less marked in the girls.

Measurements of the height of 20 000 conscripts (S. Hansen 1907–1911) showed that the average height varied according to occupation, the shortest being the tailors, average height 165 cm, and the tallest ones the students, average height 173 cm.

Broman, Dahlberg & Lichtenstein, comparing the height of children in private schools and in council schools, found the former children to be an average of about 3 cm taller than the latter.

Abrahamson (1950) in a study of the height of 871 boys in Stockholm related height to the father's income as well as to his occupation. No correlation was found between height and income, but a significant difference in height when related to occupational groups.

Dossing, whose material comprised 62,534 measurements of [illegible] 766 boys and 66 164 measurements of [illegible] 673 girls from 59 council schools and 3 grammar schools in Copenhagen, divided his material by income into well-to-do, poor and others. For boys as well as for girls, he found that the children from well-to-do families were an average of 1.5 cm taller than the children from the poor families, i.e. a difference so slight that income *per se* does not seem to influence height.

Quaade (1956) investigated the influence of income and of heredity upon the height of 3 771 children. He found

from the taxation authorities. For each family it was stated, in a code, whether for the year 1964–1965 the assessed taxable income had been between 0 and 5000 kroner between 5000 and 10,000 kr between 10 000 and 20 000 kr etc.

In the case of 3 boys and 16 girls it was not possible to procure data concerning social circumstances. Their families could not be found through the National Registry or else they were domiciled in municipalities that did not wish to supply the named information.

For comparison, Table 42 gives the distribution of assessed taxable income *for all 249 155* supporters in the municipality of Copenhagen for the year 1964–65 This table also includes supporters who have no children at school.

In order to ascertain whether differences in social circumstances influence skeletal maturation, the material was grouped by *skeletal maturation* and *occupation* in Tables 43 and 44 Skeletal maturation is given in 3 categories one group with average skeletal maturity one skeletally advanced, and one skeletally retarded. In practice, this grouping was done by picking out to represent average skeletal maturity children whose skeletal age corresponded to their chronological age in terms of whole completed years. Children whose chronological age was above their skeletal age were grouped as retarded and those who were younger than their skeletal age as advanced.

From Tables 43 and 44 it is apparent that in the higher social classes the number of children with retarded

Table 42

Assessed taxable income of all 249 155 supporters in the municipality of Copenhagen 1964–65.

Assessed taxable income	%
0– 5,000 kr	1
5–10,000 kr	20
10–20,000 kr	38
20–30,000 kr	24
> 30,000 kr	6
Total	100

...maturity and occupational groups. *Table 43*

f Clerks and shop assistants		Skilled labourers		h Unskilled labourers		Housewives		k Disablement pensioners		Total	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
31	39 2	24	27 9	33	29.2	8	34.8	0		171	36 0
19	24 1	28	32 6	[illegible]	34 5	6	26.1	0		142	30 0
29	36 7	34	39 5	41	36.3	9	39 1	0		161	34 0
[illegible]	100 0	[illegible]	100 0	113	100 0	23	100 0	0		474	100.0

...maturity and occupational groups *Table 44*

No	%	No	%	No	%	No	%	No	%	No	%
31	34 8	27	26 2	28	23 7	9	37.5	1	100.0	166	32.2
34	38 2	41	39.8	52	44 1	7	29.2	0	0	208	40.3
24	27 0	35	34.0	38	32.2	8	33.3	0	0	142	27.5
89	100 0	103	100 0	118	100 0	24	100 0	1	100.0	516	100 0

vourable social circumstances and late menarche.

It is apparent also that the less favourable social circumstances relate *more to occupation than to income*, although it cannot be said which factors are decisive.

There is no doubt that nutrition influences weight and skeletal maturation.

Finally it may be pointed out, as done by several previous authors, that social circumstances need not consist *only of external factors*" but may well contain genetic factors.

Present Studies of the Influence of Social Factors Upon Skeletal Maturation

Table 40 gives the distribution of the present material by occupation. This grouping is in accordance with Svalastoga (1959)

Table 41 lists the distribution by income. Information concerning occupation as well as income was obtained

Table 40

Distribution by supporter's occupation.

Occupation	No.	%
a Professionals	17	1 7
b Managers etc.	5?	5.3
c Teachers, artists	4	2.4
d Superior non professionals, salaried employees	183	18.5
e Small tradesmen	78	7.9
f Clerks, shop assistants	168	17 0
g Skilled labourers	189	19 1
h Unskilled labourers	231	23.3
i Housewives	47	4 7
k Disablement pensioners	1	0 1
Total	990	100.0
Unknown	19	

Table 41

Distribution by supporter's assessed taxable income 1964–65

Assessed taxable income	No.	%
0– 5 000 kr	6	0 6
5–10 000 kr	51	5.2
10–20 000 kr	403	40 7
20–30 000 kr	430	43.4
30–40,000 kr	67	6.7
> 40 000 kr	33	3 4
Total	990	100.0
Unknown	19	

Table 43

Distribution of boys by ske

Skeletal maturity	Professionals No.	Professionals %	b Managers, etc. No.	b Managers, etc. %	Teachers, artists N	Teachers, artists %	d Superior non-professionals, salaried employees No	d Superior non-professionals, salaried employees %	Small tradesmen No.	Small tradesmen %
Advanced	5	41 7	14	58.3	2	33.3	38	40.4	16	43.
Average	6	50.0	6	25.0	2	33 3	?6	27 7	10	7
Retarded	1	8.3	4	16.7		33.3	30	31 ?	11	29.
Total	12	100 0	24	100.0	6	100 0	94	100 0	37	100

Tabl 44

Distribution of girls by ske

Skeletal maturity	No	%	No.	%	No.	%	No.	%	No	%
Advanced	3	60.0	11	39.3	8	44.5	30	33 7	18	43
Average	1	20.0	10	35.7	[illegible]	33.3	41	46.1	16	39
Retarded	1	20.0	7	25.0	4	?? 2	18	?0 2	7	17
Total	5	100.0	28	100.0	[illegible]	100 0	89	100 0	41	100

Table 47

Distribution by skeletal maturity and supporter's occupation.

Boys and girls.

Skeletal maturity	I Professional, managerial, teachers, etc.		II Clerks and shop assistants		III Skilled and unskilled labourers		Total	
	N	%	No.	%	No.	%	No.	%
Advanced	145	41.0	62	37.0	112	26.7	319	33.9
Average	124	35.0	53	31.5	160	38.1	337	35.8
Retarded	85	24.0	53	31.5	148	35.2	286	30.3
Total	354	100.0	168	100.0	420	100.0	942	100.0

$\chi_4^2 = 21.9^{**}$

Table 48

Distribution by skeletal maturity and supporter' income.

Boys.

Skeletal maturity	> 20,000 kr		< 20,000 kr		Total	
	No	%	No	%	No	%
Advanced	104	40.3	59	30.6	163	36.1
Average	73	28.3	63	32.6	136	30.2
Retarded	81	31.4	71	36.8	152	33.7
Total	258	100.0	193	100.0	451	100.0

$\chi_2^2 = 4.5$

Table 49

Distribution by skeletal maturity and supporter' income.

Girls.

Skeletal maturity	> 20,000 kr		< 20,000 kr		Total	
	No	%	No	%	No	%
Advanced	91	31.5	65	29.6	156	31.8
Average	111	40.8	90	41.1	201	40.9
Retarded	70	25.7	64	29.2	134	27.3
Total	272	100.0	219	100.0	491	100.0

$\chi_2^2 = 1.1$

skeletal maturity decreases, while in the working classes it increases. Within the group of clerks and shop assistants the percentage of skeletally advanced retarded and average children is the same as in all occupational groups together

It was natural therefore, in the more detailed analysis to operate with only three social classes

(I) Professional, managerial teachers, artists, superior non-professionals, salaried employees, and small tradesmen

(II) *Clerks and shop assistants.*

(III) Skilled and unskilled labourers.

The groups of housewives and disablement pensioners were left out, as they are recruited from all social classes.

Tables 45 and 46 show for boys and girls respectively the distribution by skeletal maturity and these 3 occupational groups. With decreasing status there is an increased percentage of skeletally retarded children and a correspondingly decreasing percentage of advanced ones. This difference is significant for boys as well as girls.

When considering boys and girls in one group and this is permitted as *the distribution by parents occupation* is approximately the same for boys and

Table 45

Distribution by skeletal maturity and supporter s occupation.

Boy

Skeletal maturity	I Professional, managerial, teachers, etc.		II Clerks and shop assistants		III Skilled and unskilled labourers		Total	
	No.	%	No.	%	No	%	No.	%
Advanced	75	43 4	31	39.2	57	28.6	163	36 1
Average	50	28 9	19	24 1	67	33 7	136	30.[illegible]
Retarded	48	27 7	29	36.7	75	37 7	15	33 7
Total	173	100.0	79	100 0	199	100 0	451	100.0

$\chi_4^2 = 10.7$

Table 46

Distribution by skeletal maturity and supporter s occupation.

G l

Skeletal maturity	I Professional managerial, teachers, etc		II Clerks and shop assistants		III Skilled and unskilled labourers		Total	
	No.	%	N	%	N	%	No	%
Advanced	70	38.7	[illegible]	34 8	55	4 9	156	31 8
Average	74	40.9	34	38.[illegible]	93	42.1	201	40 9
Retarded	37	20 4	24	7 0	73	33 0	134	7 3
Total	181	100.0	89	100 0	221	100 0	491	100 0

$\chi_4^2 = 12.2$

Table 31

Distribution by skeletal maturity and by supporters' occupation and income.

Boys and girls.

Skeletal maturity	I Professional, managerial, teachers, etc				II Clerks and shop assistants				III Skilled and unskilled labourers				Total	
	> 20,000		< 20,000		> 20,000		< 20,000		> 20,000		< 20,000			
	No.	%	N	%	No	%	No	%	No	%	No.	%	No.	%
Advanced	110	43.5	35	34.6	28	35.9	34	37.8	57	28.6	55	24.9	319	33.9
Average	81	32.0	43	42.6	27	34.6	26	28.9	76	38.2	84	38.0	337	35.8
Retarded	62	24.5	23	22.8	23	29.5	30	33.3	66	33.2	82	37.1	286	30.3
Total	253	100.0	101	100.0	78	100.0	90	100.0	199	100.0	221	100.0	942	100.0
	$\chi_2^2=3.8$				$\chi_2^2=0.7$				$\chi_2^2=1.0$					

Table 50
Distribution by skeletal maturity and supporter's income
Boys and girls.

Skeletal maturity	> 20,000 kr		< 20 000 kr		Total	
	No.	%	No.	%	No.	%
Advanced	195	36.8	124	30.1	319	33.9
Average	184	34 7	153	37 1	337	35.8
Retarded	151	28.5	135	32.8	286	30,3
Total	530	100.0	412	100.0	942	100.0

$\chi_2^2 = 4.9$

girls we find an even clearer significance beyond the 0 1 % limit (Table 47)

Also, it was investigated whether the *income* influenced skeletal maturation (Tables 48 and 49) In these tables all persons with assessed taxable incomes below 20 000 kroner (about £ 1 000) are assembled in one group and all with incomes above 20 000 in another This limit was not fixed at a lower level, as the group with an income below 10 000 kroner in the relevant occupational groups comprised only 38 families.

For boys as well as girls there is a tendency for the percentage with retarded skeletal maturity to rise with decreasing income, but this difference is not significant, also not when calculated for girls and boys together (Table 50) χ^2 is 4 9 and ought to be 6 0 to be significant. In other words, it was not possible to demonstrate that the income had a significant influence upon skeletal maturation.

Within the individual occupational groups there was also no significant dependence between skeletal maturity and income (Table 51)

Tables 52 53 and 54 show for boys, girls, and both sexes, the skeletal maturity according to whether or not their *mothers were employed* No significant dependence was found not either within the individual occupational groups (Table 55)

Lastly it was analysed whether a dependence could be found between skeletal maturity and *crowded flats* defined as flats or houses occupied by at least 2 persons per room Tables 56 57 and 58 show the distribution for boys, girls, and both sexes.

As far as the boys are concerned there is a significantly larger number of skeletally retarded among those from crowded flats. The girls show the same tendency but among them the findings are not significant. When boys and girls are considered together there is a significantly larger number of skeletally retarded children in crowded flats.

In an attempt to ascertain whether housing *per se is a factor of influence* and to investigate whether children with poor housing are socially worse off also in other respects—as this might increase the tendency to retardation

Table 51

Distribution by skeletal maturity and by supporter's occupation and income.

Boys and girls.

Skeletal maturity	I Professional, managerial, teachers, etc.				II Clerks and shop assistants				III Skilled and unskilled labourers				Total	
	> 20,000		< 20,000		> 20,000		< 20,000		> 20,000		< 20,000			
	No	%	No	%	No	%	No.	%	N	%	No	%	No.	%
Advanced	110	43.5	35	34.6	28	35.9	34	37.8	57	28.6	55	24.9	319	33.9
Average	81	32.0	43	42.6	27	34.6	26	28.9	76	38.2	84	38.0	337	35.8
Retarded	[illegible]	24.5	23	22.8	[illegible]	29.5	30	33.3	66	33.2	82	37.1	286	30.3
Total	253	100.0	101	100.0	78	100.0	90	100.0	199	100.0	221	100.0	942	100.0
	$\chi_2^2 = 3.8$				$\chi_2^2 = 0.7$				$\chi_2^2 = 1.0$					

Table 50

Distribution by skeletal maturity and supporter's income

Boys and girls.

Skeletal maturity	> 20,000 kr		< 20,000 kr		Total	
	No.	%	No.	%	No.	%
Advanced	195	36.8	124	30.1	319	33.9
Average	184	34.7	153	37.1	337	35.8
Retarded	151	28.5	135	32.8	286	30.3
Total	530	100.0	412	100.0	942	100.0

$\chi_2^2 = 4.9$

girls, we find an even clearer significance, beyond the 0.1 % limit (Table 47).

Also it was investigated whether the *income* influenced skeletal maturation (Tables 48 and 49). In these tables all persons with assessed taxable incomes below 20 000 kroner (about £ 1 000) are assembled in one group and all with incomes above 20 000 in another. This limit was not fixed at a lower level as the group with an income below 10 000 kroner in the relevant occupational groups comprised only 38 families.

For boys as well as girls there is a tendency for the percentage with retarded skeletal maturity to rise with decreasing income, but this difference is not significant, also not when calculated for girls and boys together (*Table 50*). χ^2 is 4.9 and ought to be 6.0 to be significant. In other words, it *was not possible to demonstrate that* the income had a significant influence upon skeletal maturation.

Within the individual occupational groups there was also no significant *dependence* between skeletal maturity and income (Table 51).

Tables 52, 53 and 54 show for boys, girls, and both sexes, the skeletal *maturity according to whether or not* their *mothers were employed*. No significant dependence was found, not either within the individual occupational groups (Table 55).

Lastly it was analysed whether a dependence could be found between skeletal maturity and *crowded flats* defined as flats or houses occupied by at least 2 persons per room. Tables 56, 57 and 58 show the distribution for boys, girls, and both sexes.

As far as the boys are concerned there is a significantly larger number of skeletally retarded among those from crowded flats. The girls show the same tendency, but among them the findings are not significant. When boys and girls are considered together there is a significantly larger number of skeletally retarded children in crowded flats.

In an attempt to ascertain whether housing *per se* is a factor of influence and to investigate whether children with poor housing are socially worse off also in other respects—as this might increase the tendency to retardation—

Table 55

Distribution by skeletal maturity supporters' occupation and mother employment.

Boys and girls.

Skeletal maturity	I Professional, managerial, teachers, etc				II Clerks and shop assistants				III Skilled and unskilled labourers				Total	
	Mother at home		Mother out		Mother at home		Mother out		Mother at home		Mother out			
	No	%	No	%	No	%	No.	%	No.	%	No.	%	No.	%
Advanced	88	40.8	57	41.3	19	33.8	43	37.4	37	23.9	73	28.5	319	33.9
Average	78	36.1	46	33.3	21	39.6	32	27.8	61	39.4	99	37.4	337	35.8
Retarded	50	23.1	35	25.4	13	21.6	40	34.8	57	36.7	91	34.3	286	30.3
Total	216	100.0	138	100.0	53	100.0	115	100.0	155	100.0	263	100.0	942	100.0
	$\chi^2_2=0.4$				$\chi^2_2=2.8$				$\chi^2_2=1.0$					

Table 52

Distribution by skeletal maturity and by mother's employment.

Boys

Skeletal maturity	Mother at home		Mother out		Total	
	No.	%	No.	%	N	%
Advanced	78	40.0	85	33.2	163	36.1
Average	60	30.8	76	29.7	136	30.2
Retarded	57	29.2	95	37.1	152	33.7
Total	195	100.0	256	100.0	451	100.0

$\chi_S^2=3.5$

Table 53

Distribution by skeletal maturity and by mother's employment.

Girls

Skeletal maturity	Mother at home		Mother out		Total	
	No.	%	No.	%	No.	%
Advanced	66	28.8	90	34.4	156	31.8
Average	100	43.7	101	38.5	201	40.9
Retarded	63	27.5	71	27.1	134	7.3
Total	229	100.0	26[illegible]	100.0	491	100.0

$\chi_S^2=1.9$

Table 54

Distribution by skeletal maturity and by mother's employment

Boys and girls

Skeletal maturity	Mother at home		Mother out		Total	
	No.	%	No.	%	No.	%
Advanced	144	34.0	175	33.8	319	33.9
Average	160	37.7	177	34.2	337	35.8
Retarded	120	28.3	166	32.0	286	30.3
Total	424	100.0	518	100.0	9[illegible]	100.0

$\chi_S^2=1.9$

Table 59

Distribution by skeletal maturity occupation, and crowded/non-crowded flats.

Boys and girls.

Skeletal maturity	Occupational groups I+II				Occupational group III			
	Non-crowded		Crowded		Non-crowded		Crowded	
	No.	%	No	%	No	%	No	%
Advanced	196	39.2	11	47.8	92	27.1	20	24.7
Average	170	34.1	7	30.4	137	40.4	23	28.4
Retarded	133	26.7	5	21.8	110	32.5	38	46.9
Total	499	100.0	23	100.0	339	100.0	81	100.0
	$\chi^2_2 = 0.7$				$\chi^2_2 = 6.5$			

the material was further sub-divided by skeletal maturity housing, and occupation (Table 59).

This revealed that in the upper social classes crowding does not increase the tendency to retardation, while in the lower social classes crowding is of a distinct significance.

Conclusion

With falling social status the percentage of skeletally retarded children increases significantly.

In addition, there is a tendency for the percentage of retarded children to increase with decreasing income, but this difference is not significant.

The children's skeletal maturation is not demonstrably influenced by whether or not their mothers are employed.

Children living in crowded flats are skeletally more retarded than children living in non-crowded flats, but this applies only to the occupational group of skilled and unskilled labourers.

Table 56

Distribution by skeletal maturity and crowded/non-crowded flats.

Boys

Skeletal maturity	Non-crowded No.	%	Crowded No.	%	Total No.	%
Advanced	145	36.3	18	35.3	163	36.1
Average	127	31 7	9	17 6	136	30 2
Retarded	128	32 0	24	47 1	152	33.7
Total	400	100 0	51	100 0	451	100.0

χ =6 0

Table 57

Distribution by skeletal maturity and crowded/non-crowded flats.

Girls

Skeletal maturity	Non-crowded No.	%	Crowded No.	%	Total No.	%
Advanced	143	32 7	13	4.5	156	31.8
Average	180	41 1	21	39 6	201	40.9
Retarded	115	26 2	19	35.8	134	27.3
Total	438	100.0	53	99.9	491	100.0

χ_2=2 6

Table 58

Distribution by skeletal maturity and crowded/non-crowded flats.

Boys and girls.

Skeletal maturity	Non-crowded No.	%	Crowded No.	%	Total No.	%
Advanced	288	34 4	31	29.8	319	33.8
Average	307	36.6	30	28 8	337	35.8
Retarded	43	29 0	43	41 4	286	30 4
Total	838	100 0	104	100 0	942	100.0

χ^2_2=6.8

British material represents a wide section of all social classes.

Tanner & Whitehouse's system does not appear to afford a more accurate assessment than does Greulich & Pyle's atlas, even though each individual bone is rated according to its assessed maturity. The standard deviation of the skeletal age assessment is the same with Tanner & Whitehouse's method as with Greulich & Pyle's. The difference between skeletal age and chronological age also varies in the different age groups when the Tanner & Whitehouse system is used. The reason why Tanner & Whitehouse's system does not permit a more accurate determination of skeletal age is presumably that their rating system, in the form recommended so far, does not pay sufficient regard to differences in the growth rate of the individual bones at different times (cf. pp. 41–42).

Practical Application of Skeletal Age Assessment

In practice, the skeletal age may be assessed on a single X-ray film with an accuracy of about 6 months. Such a single assessment is required when a child's general maturity is to be evaluated, e.g. in certain endocrine disturbances, but also for cross-sectional studies of the development of children and adolescents in a population.

Reading of a series of X-ray films of the hand skeleton taken of the same child at intervals of e.g. 6 months allows a more accurate assessment of skeletal maturity than does a single reading, because in serial films it is possible to compare the sequence in a development. This procedure may be used when a given child's skeletal maturation is to be followed, for instance because a child is retarded, and treatment is being administered to accelerate the development. Frequently this is hormone therapy of children with endocrine disturbances.

Assessment of skeletal age is used also in trying to predict a child's adult height. By Bayley-Pinneau's height tables it is possible, at least for normal children, to predict with fair accuracy the adult height, if the child's height and skeletal age, according to Greulich & Pyle's atlas, are known. This method is too inaccurate for children under 6–7 years of age. The importance of being able to predict the adult height may be exemplified by the fact that Tanner has investigated children from the Royal Ballet School and can predict the adult height with an accuracy of a few cm. Therefore, children who are estimated to attain an adult height outside the permitted limits can stop attending the ballet school.

Factors Influencing Skeletal Maturation

Severe disease (Dreizen et al. 1954), heredity (Pryor 1907, Reynolds 1943, Reynolds & Schoen 1947), sex, hormone production, and social circumstances are assumed to influence skeletal maturation. Children with severe diseases were excluded from the present material. The influence of genetic factors upon skeletal maturation may perhaps be indirectly estimated by

Chapter 15

Discussion and Conclusions

Assessment of Skeletal Age

The present study has shown that Greulich & Pyle's atlas is applicable for the assessment of skeletal age in Danish children. However, the skeletal maturity in the present material of school children, close to the socio-economic average in Copenhagen, was retarded by an average of about 6 months in relation to the American children who formed the basis of Greulich & Pyle's atlas.

In using the Greulich & Pyle atlas on Danish children, therefore, it must be borne in mind that a child of average maturity has a skeletal age which is about 6 months below its chronological age.

The reason why the children in Copenhagen are skeletally retarded as compared with the American children is presumably that the children of the American material were recruited from homes that were in all respects above average. The maturation of these children, examined a generation ago, took place even earlier than the present average maturation of American children.

The average skeletal retardation in the present material was 5.9 months for boys and 5.2 months for girls, in some age groups somewhat lesser, in others greater. This variation in the difference between skeletal and chronological age, also apparent in other studies (Greulich 1951, 1957), may be due to some heterogeneity in the assessment, since skeletal age is easier to assess in some age groups than in others. This means that where certain skeletal ages are concerned a systematic error may have been introduced, an error which changes only the mean value without influencing the standard deviation.

However, the variation in the difference between skeletal and chronological age may also be due to some heterogeneity of the materials. All the standards in Greulich & Pyle's atlas are perhaps not equally representative of the age group which they are supposed to represent, and the skeletal maturity in a single age group of the present material might happen to be more—or less—retarded than the average for the entire material.

The use of Tanner & Whitehouse's system for assessing skeletal development showed the skeletal maturity in the present material to be advanced by an average of 2.3 months in relation to the children on whom Tanner & Whitehouse based their method. The

voice are concerned, the difference is significant, and for the beard the tendency to a higher correlation to skeletal age than to chronological age is very distinct. Such a correlation was indeed to be expected, as both skeletal maturation and the appearance of the various puberal signs in boys are due to the androgen production in the testes and adrenals. The fact that for the *beard* there was only a tendency to a higher correlation to skeletal than to chronological age, and not a significant difference, may be due to inaccuracy in the measurement and to individual factors of genetic nature.

For *breast* development no significantly higher correlation to skeletal than to chronological age was found. The explanation may be difficulty in assessing the degree of breast development. The size and shape of the breasts are also influenced by inherited factors. Lastly the maturation of the breast is influenced not only by oestrogenic hormone, but also by prolactin, progesterone, and growth hormone which exert very little or no effect upon skeletal maturation.

That a dependence exists at all between the various maturational criteria and chronological age, when skeletal age is held constant, may be explained largely by the error of measurement in assessing skeletal age (cf pp. 62–63)

Thus, skeletal age is a better measure than chronological age of the stage of biological maturation. Skeletal age is also a better measure than height. The explanation is that a given skeletal age indicates how far a child has reached in the process of maturation, which terminates in closure of all epiphyses. On the other hand a given height does not indicate how great a percentage of its final height the child has attained, as its adult height is not known until the growth in length is completed. The various signs of puberty separately and together give a certain impression of the stage of development, but it is rather difficult to grade these criteria of maturity Therefore, determination of skeletal age is definitely justified in assessing biological maturity

Skeletal Maturation in Relation to Social Conditions

In the present study skeletal maturity was related to the supporter's occupation, to his assessed taxable income, to housing, and to the mother's employment, if any

With decreasing occupational status a significantly increasing percentage of children showed retarded skeletal maturity There was also a tendency for the percentage of children of retarded skeletal maturity to increase with decreasing income, but no significance was demonstrated. Furthermore, skeletal maturation in children living in crowded flats proved to be more retarded than in children from non-crowded flats. However this applies only to children whose fathers were of occupational group III skilled and unskilled labourers. Analysis of skeletal maturity according to whether or not the mothers were employed showed no significant difference.

These findings indicate that skeletal maturation, and thus also biological maturation in children of an average

comparing the pattern of growth and development of children with that of their parents, but the parents data carry considerable inaccuracy

Relation of Skeletal Maturation to Height and Sexual Development

As hormone production influences growth in height, sexual development, as well as skeletal maturation it seemed natural to study the relationship of various developmental criteria to skeletal maturation

Thyroid hormone is necessary for normal skeletal development. Primarily it appears to act upon the maturation of the bones and thus their shape, but—together with the growth hormone—it also causes longitudinal growth of the bones. The growth hormone is not believed to accelerate skeletal maturation.

The role of the sex hormones in skeletal maturation is presumably that androgens, from the adrenals as well as from the testes, accelerate growth in length in the epiphyses, but to an even greater extent skeletal maturation, including epiphyseal closure. Oestrogenic hormone accelerates epiphyseal closure (Wilkins 1965 Talbot, Sobel McArthur & Crawford 1952)

In the present study it was found that the various maturational criteria such as height menarche, breast development, pubic hair etc. occur at a skeletal age which according to the atlas of Greulich & Pyle, is about 6 months below the chronological age. This is in keeping with the fact that the present children were skeletally retarded by about 6 months as compared with the American material.

Moreover it was confirmed that a higher correlation exists between height and skeletal age than between height and chronological age and a higher correlation between sexual development and skeletal age than between sexual development and chronological age

The finding of a significantly higher correlation between *height increment and skeletal maturation than between* height gain and chronological age is explicable by the decisive influence of the thyroid hormone, growth hormone, and sex hormones upon body height as well as skeletal maturation.

A significantly higher correlation was found between the onset of *menarche* and skeletal age than between menarche and chronological age. This accords with the fact that the menarche is governed by the production of oestrogen which is also of importance to epiphyseal closure.

Furthermore, there was a significantly higher correlation between appearance of *pubic hair* and skeletal age than between pubic hair and chronological age—in boys as well as in girls. The explanation is presumably that androgens from the adrenal cortex in girls and androgens from the adrenal cortex and testes in boys influence the development of pubic hair as well as skeletal maturation.

In respect to the development of the *testes* the *change of voice* and *growth of beard* there was also a higher correlation to skeletal age than to chronological age. As far as the testes and the

voice are concerned, the difference is significant, and for the beard the tendency to a higher correlation to skeletal age than to chronological age is very distinct. Such a correlation was indeed to be expected, as both skeletal maturation and the appearance of the various puberal signs in boys are due to the androgen production in the testes and adrenals. The fact that for the *pubic hair* there was only a tendency to a higher correlation to skeletal than to *chronological age, and not a significant* difference, may be due to inaccuracy in the measurement and to individual factors of genetic nature.

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These findings *indicate that* skeletal maturation, and thus also biological maturation in children of an average

socio-economic level in Copenhagen depends but slightly upon the supporter's income, but to a far greater extent upon his occupation

A difference in the incidence of illness in the various occupational groups might explain this difference in skeletal maturation However this is unlikely as it has been demonstrated that only severe diseases influence skeletal maturation—and children with severe diseases were excluded from the present study

This dependence of skeletal maturation upon occupation is more likely to be due to the fact that different occupational groups have different ways of living Very probably there is a question of a difference in nutrition (cf p 103), but this can only be proved by long lasting well-controlled dietary analyses.

Summary

In the *introduction* the extent and aim of the study are described. The investigations consisted of a cross-sectional study of skeletal maturation of the hand and wrist in a series of Danish school children aged 7–18 years. An attempt was made to correlate skeletal maturity to chronological age, height, stage of sexual development, and the environment in which the children were raised. The results were compared with those of corresponding studies from other countries.

The object of the study was to investigate whether various foreign systems for skeletal age assessment are applicable to Danish children. The value of skeletal maturity as a measure of biological maturity was studied, and lastly it was evaluated whether the differences in social circumstances found in this material influenced the skeletal maturation.

Chapter 1 gives a review of previous studies on the skeletal maturation of the hand and wrist, in particular the onset and sequence of ossification centres and of epiphyseal fusion with the shafts. Various systems for assessing skeletal age are based upon the skeletal maturation in the hand, foot, knee, or hip or in the six areas hip, knee foot, shoulder elbow and hand Particular attention is given to Greulich & Pyle's atlas and Tanner & Whitehouse's system for estimating the maturity of the hand skeleton—the two methods applied to the present material The reasons for studying skeletal maturation in the hand and wrist are advanced

Chapter 2 deals with the methods for assessing the development of various sex characters in boys and girls.

Chapter 3 presents the material which comprises 477 boys and 532 girls in the age range 7–18 years.

Chapter 4 describes the method, i.e. examination by X-ray of the right hand, measurement of standing height and for the boys measurement of the length of the testes and penis and assessment of the stage of pubic hair development, moustache and voice—for the girls history-taking of the time of menarche and assessment of the stage of breast and pubic hair development.

In *chapter* 5 the procedure of assessing skeletal age by the atlas of Greulich & Pyle and by the method of Tanner & Whitehouse are described. Certain difficulties in assessing the carpal bones by the latter method are demonstrated.

Chapter 6 submits the results of

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on the age at menarche. It is clearly apparent that the menarche is occurring ever earlier The age at menarche for the girls of the present series averaged 13 /4 years in terms of chronological age and $12^{3}/_{4}$ *in terms of skeletal age*. This difference of [illegible] months is due to the fact that skeletally the Danish material was retarded by about 6 months in relation to the Brush Foundation material.

There is a significantly higher correlation between skeletal age and age at menarche than between chronological age and age at menarche.

Chapter 9 deals with the development of the breasts. In the girls of the present material this development started, on the average, at a chronological age of 10.8 years and a skeletal age of 10.2 years. As far as breast maturation is concerned too there was a tendency to a greater dependence upon skeletal than upon chronological age, but this difference is not significant.

Chapter 10 deals with the development of pubic hair In the girls it appears on the average at a chronological age of 11.6 years and a skeletal age of 11.0 years. In the boys of the present series pubic hair started appearing at an average chronological age of 12.8 years and skeletal age 12.4 years. For girls as well as boys there was a significantly higher correlation between pubic hair and chronological age.

Chapter 11 submits the results of measurements of the testes. The peak increment took place in the age 11–14 years. It applies to this age group that the correlation between testicular growth and skeletal age was significantly higher than between testicular growth and chronological age.

From *chapter 12* it is apparent that the growth of the penis takes place mainly at the age 12–15 years. There is a tendency to a higher correlation between increase in penis size and skeletal age than between increase in penis size and chronological age, but the difference is not significant.

In *chapter 13* it is reported that the voice change occurred in the boys of the present series at an average chronological age of $15^{1}/_{4}$ years, skeletal age 15 years. A moustache appears on the average at chronological age $14^{1}/_{4}$ years and skeletal age $13^{3}/_{4}$ years. There is a significantly higher correlation between voice change and skeletal age than between voice change and chronological age. There is a marked tendency for the appearance of a moustache to be more closely correlated to skeletal than to chronological age, but a significant difference could not be demonstrated.

Chapter 14 first gives an account of various factors, such as heredity nutrition, disease, and hormone production, which may influence maturation, including skeletal maturation. In the present study skeletal maturation was considered in relation to supporter's occupation, assessed taxable income, housing and to mother's employment, if any With decreasing occupational status there was a significantly increasing percentage of children of retarded skeletal maturity There was also a tendency for the percentage of retarded children to increase with decreasing income, but no significance was demonstrated.

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According to Greulich & Pyle's atlas the boys of the present series are retarded by an average of 5.9 months in relation to the material upon which the atlas was based and the girls by an average of 5.2 months.

Assessed by the method of Tanner & Whitehouse the present material is advanced by an average of 2.3 months in relation to the children examined by Tanner & Whitehouse. This applies to boys as well as to girls. The standard deviation of the skeletal age determination by the atlas of Greulich & Pyle is 12.4 months for boys and 11.5 months for girls and by the method of Tanner & Whitehouse 13.0 months for boys and 10.8 months for girls. These values represent the average for all the studied age groups. The standard deviation comprises biological variation and error of measurement. The observed standard deviation is in the same range as reported by previous authors.

The variable error of the skeletal age assessment by the Greulich & Pyle atlas in the present material was 3–4 months, i.e. in the same range as found by others.

In the further investigations it was preferred to use the results of skeletal age assessment by the atlas of Greulich & Pyle, partly because this method is simple and quick to learn and use and partly because in the present study it proved just as accurate as the system of Tanner & Whitehouse.

In *chapters 7–13* an attempt is made to evaluate to what extent skeletal age is applicable as a measure of biological maturity by comparing it with other maturational criteria such as height, menarche, development of breasts and pubic hair etc..

The assessment of skeletal age as a measure of biological maturity was done by comparing the relation of the various maturational criteria to skeletal age with the relation of the same criteria to chronological age.

The curves illustrating the relation of the various maturational criteria to chronological age may be taken to represent normal development, in so far as it may be assumed that the present material is a representative section of children in the Danish population. The curves represent a snapshot of the development, as the study was cross-sectional.

In *chapter 7* various Norwegian, Swedish and American height tables are compared with the result of the present height measurements. The children of the present material were, measured in height years, about 6 months retarded in relation to the children of the Brush Foundation material which formed the basis of Greulich & Pyle's atlas. A significantly higher correlation was found between height and skeletal age than between height and chronological age

Chapter 8 reports previous studies

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Resumé

I *indledningen* gøres rede for arbejdets omfang og formål. Arbejdet omfatter en tværsnitsundersøgelse af skeletmodningen i hånd og håndled hos en række danske skolebørn i alderen 7 til 18 år. Knogleudviklingen er søgt korreleret til børnenes kronologiske alder, pubertetsudvikling og det miljø, hvori de er vokset op. De fundne resultater er sammenlignet med tilsvarende udenlandske.

Hensigten med arbejdet har været at undersøge, om forskellige udenlandske systemer til skeletalderbestemmelse kan anvendes på danske børn. Knogleudviklingens værdi som mål for børnenes biologiske udvikling undersøges, og endelig vurderes, om de i materialet fundne forskelle i sociale forhold har indflydelse på skeletudviklingen.

I *kapitel I* refereres tidligere undersøgelser over skeletudviklingen i hånd og håndled, specielt tidspunkterne og rækkefølgen for knoglekernernes optræden og for epifysernes sammenvoksning med diafyserne. Derefter omtales forskellige systemer til skeletalderbestemmelse, der bygger på knogleudviklingen i hånd, fod, knæ, hofte eller de seks områder hofte, knæ, fod, skulder albue og hånd. Greulich & Pyle s atlas og Tanner & Whitehouse s system til bestemmelse af håndskelet udviklingen gennemgås specielt, da det er disse to metoder der er anvendt på nærværende materiale. Det begrundes, at man specielt har valgt at undersøge skeletudviklingen i hånd- og håndled.

I *kapitel II* gennemgås metoder til vurdering af forskellige kønskarakterers udvikling hos drenge og piger

I *kapitel III* beskrives materialet, som består af 477 drenge og 532 piger i alderen 7 til 18 år

Kapitel IV indeholder beskrivelse af undersøgelsen, som omfattede røntgenfotografering af højre hånd, måling af stående højde, endvidere for drengenes vedkommende måling af testes' og penis længde samt vurdering af pubesbehåring, moustache og stemme, og for pigernes vedkommende anamnese vedrørende menarchens indtræden samt vurdering af mammaudvikling og pubesbehåring

I *kapitel V* redegøres for fremgangsmåden ved skeletalderbestemmelsen efter Greulich & Pyle s atlas og Tanner & Whitehouse s metode. Der påvises visse vanskeligheder ved vurdering af håndrodsknoglerne efter sidstnævnte metode.

I *kapitel VI* fremlægges resultaterne af skeletalderbestemmelsen efter Greulich & Pyle s atlas og Tanner & Whitehouse s metode. Der er angivet [illegible] serier

The skeletal maturation of children living in crowded flats was found to be more retarded than in children from non-crowded flats, but this applies only to children whose fathers belonged to occupational group III skilled and unskilled labourers

Analysis of skeletal maturation according to whether or not the mothers were employed showed no significant difference.

Chapter 15 comprises discussion and conclusions.

Resumé

I *indledningen* gøres rede for arbejdets omfang og formål. Arbejdet omfatter en tværsnitsundersøgelse af skeletmodningen i hånd og håndled hos en række danske skolebørn i alderen 7 til 18 år. Knogleudviklingen er søgt korreleret til børnenes kronologiske alder, pubertetsudvikling og det miljø, hvori de er vokset op. De fundne resultater er sammenlignet med tilsvarende udenlandske.

Hensigten med arbejdet har været at undersøge, om forskellige udenlandske systemer til skeletalderbestemmelse kan anvendes på danske børn. Knogleudviklingens værdi som mål for børnenes biologiske udvikling undersøges, og endelig vurderes, om de i materialet fundne forskelle i sociale forhold har indflydelse på skeletudviklingen.

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I *kapitel V* redegøres for fremgangsmåden ved skeletalderbestemmelsen efter Greulich & Pyle's atlas og Tanner & Whitehouse's metode. Der påvises visse vanskeligheder ved vurdering af håndrodsknoglerne efter sidstnævnte metode.

I *kapitel VI* fremlægges resultaterne af skeletalderbestemmelsen efter Greulich & Pyle's atlas og Tanner & Whitehouse's metode. Der er angivet 2 serier

The skeletal maturation of children living in crowded flats was found to be more retarded than in children from non-crowded flats, but this applies only to children whose fathers belonged to occupational group III skilled and unskilled labourers.

Analysis of skeletal maturation according to whether or not the mothers were employed showed no significant difference.

Chapter 15 comprises discussion and conclusions.

træder tidligere og tidligere. Menarchealderen for pigerne i nærværende materiale er gennemsnitligt 13¹/₄ år målt i kronologisk alder og 12/₄ år målt i skeletalder. Forskellen på ¹/₂ år skyldes det forhold, at det danske materiale skeletmæssigt er retarderet med ca. ¹/₂ år i forhold til Brush Foundation materialet.

Der er signifikant større korrelation mellem skeletalder og menarchealder end mellem kronologisk alder og menarchealder.

Kapitel IX omhandler mammaudviklingen. Den begynder for nærværende materiales piger gennemsnitligt ved en kronologisk alder på 10,6 år og ved en skeletalder på 10,2 år. Man finder også for mammaudviklingens vedkommende en tendens til større afhængighed af skeletalder end af kronologisk alder, men forskellen er ikke signifikant.

Kapitel X omhandler pubesudviklingen. For pigernes vedkommende begynder den gennemsnitligt ved en kronologisk alder på 11,6 år og ved en skeletalder på 11,0 år. For drengenes vedkommende finder man for nærværende materiale, at pubesudviklingen gennemsnitligt begynder ved en kronologisk alder på 12,8 år og ved en skeletalder på 12,4 år. For såvel piger som drenge finder man en signifikant større korrelation mellem pubesudvikling og skeletalder end mellem pubesudvikling og kronologisk alder.

I *kapitel XI* fremlægges resultaterne af målinger af testes. Tilvæksten er størst i 11–14 års alderen. For denne aldersgruppes vedkommende gælder det, at der er signifikant større korrelation mellem testes vækst og skeletalder end mellem testes vækst og kronologisk alder.

Af *kapitel XII* fremgår, at væksten af penis især foregår i 12–15 års alderen. Der ses tendens til større korrelation mellem vækst af penis og skeletalder end mellem vækst af penis og kronologisk alder, men forskellen er ikke signifikant.

Af *kapitel XIII* fremgår, at stemmen hos drengene i nærværende materiale går i overgang ved en gennemsnitlig kronologisk alder på 15 ¹/₂ år og ved skeletalderen 15 år. Moustache fremkommer gennemsnitligt ved den kronologiske alder 14³/₄ år og ved skeletalderen 13³/₄ år. Der er signifikant større korrelation mellem stemmens overgang og skeletalder end mellem stemmens overgang og kronologisk alder. Der er en stærk tendens til, at fremkomsten af moustache er nærmere korreleret til skeletalder end til kronologisk alder, men der påvises ingen signifikans.

I *kapitel XIV* gøres først rede for forskellige faktorer som arv, ernæring, sygdom og hormonproduktion, der kan påvirke udviklingen, derunder skeletudviklingen. I nærværende undersøgelse har man sat skeletudviklingen i relation til forsørgerens erhverv, hans ansatte skattepligtige indkomst, til boligens størrelse samt til, hvorvidt moderen havde udeerhverv eller ej. Med faldende erhvervsmæssig status påviser man en signifikant større procentdel børn med retarderet knogleudvikling. Der findes også en tendens til, at procenten af retarderede stiger med faldende indkomst, men der påvises ingen signifikans.

Man finder videre, at knogleudviklin-

for skeletaldre, bedømt efter Tanner & Whitehouse s system. De er identiske for de lave aldre, men fra det fyldte 13 år for drengenes vedkommende og det fyldte 11 år for pigernes vedkommende er der foretaget en ny vurdering fordi vurderingen af håndrodsknoglerne var behæftet med visse vanskeligheder

Efter Greulich & Pyle s atlas er drengene i nærværende materiale retarderet med gennemsnitligt 5 9 måneder i forhold til materialet der ligger til grund for atlas, og pigerne med gennemsnitligt 5,2 måneder

Bedømt efter Tanner & Whitehouse s metode er nærværende materiale avanceret med gennemsnitligt 2,3 måneder i forhold til de af Tanner & Whitehouse undersøgte børn. Det gælder for både drenge og piger

Spredningen på skeletalderbestemmelsen, foretaget efter Greulich & Pyle s atlas, er 12 4 måneder for drenge og 11,5 måneder for piger og efter Tanner & Whitehouse s metode 13 0 måneder for drenge og 10 8 måneder for piger Tallene angiver gennemsnit for alle de undersøgte aldersgrupper Spredningen omfatter biologisk variation og målefejl. Den fundne spredning er af samme størrelsesorden som i tidligere arbejder

Den variable fejl på skeletalderbestemmelsen efter Greulich & Pyle s atlas i nærværende undersøgelse er 3–4 måneder og af samme størrelsesorden som hos andre undersøgere.

I det videre arbejde har man foretrukket at anvende resultaterne af skeletalderbestemmelsen foretaget efter Greulich & Pyle s atlas, dels fordi det er en simpel og hurtig metode at indøve og anvende, dels fordi den i nærværende undersøgelse har vist sig at være lige så nøjagtig som Tanner & Whitehouse s system

I *kapitlerne VII–XIII* har man søgt at vurdere i hvor høj grad skeletalderen kan anvendes som mål for den biologiske udvikling idet man har sammenholdt den med andre udviklingskriterier som højde, indtræden af menarche mamma og pubesudvikling m. m..

Vurderingen af skeletalder som mål for den biologiske udvikling foregår ved at sammenligne de forskellige udviklingskriteriers relation til skeletalderen med de samme kriteriers relation til den kronologiske alder

Kurverne over de forskellige udviklingskriteriers relation til den kronologiske alder kan tages som udtryk for den normale udvikling for så vidt som man kan antage, at nærværende materiale er et repræsentativt udsnit af børnene i den danske befolkning Kurverne viser et øjebliksbillede af udviklingen, idet undersøgelsen er udført som en tværsnitsundersøgelse.

I *kapitel VII* sammenlignes forskellige norske, svenske og amerikanske højdetabeller med resultatet af nærværende undersøgelses højdemålinger Børnene i nærværende undersøgelse er målt i højdeår ca. et halvt år retarderet i forhold til børnene i Brush Foundation materialet, som ligger til grund for Greulich & Pyle s atlas. Der er på vist signifikant større korrelation mellem højde og skeletalder end mellem højde og kronolgisk alder

I *kapitel VIII* refereres tidligere undersøgelser over menarchealderen. Det fremgår tydeligt at menarchen ind

træder tidligere og tidligere. Menarchealderen for pigerne i nærværende materiale er gennemsnitligt $13^1/_4$ år målt i kronologisk alder og $12^3/_4$ år målt i skeletalder. Forskellen på $^1/_2$ år skyldes det forhold, at det danske materiale skeletmæssigt er retarderet med ca. $^1/_2$ år i forhold til Brush Foundation materialet.

Der er signifikant større korrelation mellem skeletalder og menarchealder end mellem kronologisk alder og menarchealder.

Kapitel IX omhandler mammaudviklingen. Den begynder for nærværende materiales piger gennemsnitligt ved en kronologisk alder på 10,8 år og ved en skeletalder på 10,2 år. Man finder også for mammaudviklingens vedkommende en tendens til større afhængighed af skeletalder end af kronologisk alder, men forskellen er ikke signifikant.

Kapitel X omhandler pubesudviklingen. For pigernes vedkommende begynder den gennemsnitligt ved en kronologisk alder på 11,6 år og ved en skeletalder på 11,0 år. For drengenes vedkommende finder man for nærværende materiale, at pubesudviklingen gennemsnitligt begynder ved en kronologisk alder på 12,8 år og ved en skeletalder på 12,4 år. For såvel piger som drenge finder man en signifikant større korrelation mellem pubesudvikling og skeletalder end mellem pubesudvikling og kronologisk alder.

I *kapitel XI* fremlægges resultaterne af målinger af testes. Tilvæksten er størst i 11–14 års alderen. For denne aldersgruppes vedkommende gælder det, at der er signifikant større korrelation mellem testes' vækst og skeletalder end mellem testes' vækst og kronologisk alder.

Af *kapitel XII* fremgår, at væksten af penis især foregår i 12–15 års alderen. Der ses tendens til større korrelation mellem vækst af penis og skeletalder end mellem vækst af penis og kronologisk alder, men forskellen er ikke signifikant.

Af *kapitel XIII* fremgår, at stemmen hos drengene i nærværende materiale går i overgang ved en gennemsnitlig kronologisk alder på $15\,^1/_2$ år og ved skeletalderen 15 år. Moustache fremkommer gennemsnitligt ved den kronologiske alder $14^1/_4$ år og ved skeletalderen $13^3/_4$ år. Der er signifikant større korrelation mellem stemmens overgang og skeletalder end mellem stemmens overgang og kronologisk alder. Der er en stærk tendens til, at fremkomsten af moustache er nærmere korreleret til skeletalder end til kronologisk alder, men der påvises ingen signifikans.

I *kapitel XIV* gøres først rede for forskellige faktorer som arv, ernæring, sygdom og hormonproduktion, der kan påvirke udviklingen, derunder skeletudviklingen. I nærværende undersøgelse har man sat skeletudviklingen i relation til forsørgerens erhverv, hans ansatte skattepligtige indkomst, til boligens størrelse samt til, hvorvidt moderen havde udeerhverv eller ej. Med faldende erhvervsmæssig status påviser man en signifikant større procentdel børn med retarderet knogleudvikling. Der findes også en tendens til, at procenten af retarderede stiger med faldende indkomst, men der påvises ingen signifikans.

Man finder videre, at knogleudviklin-

for skeletaldre, bedømt efter Tanner & Whitehouse's system. De er identiske for de lave aldre, men fra det fyldte 13 år for drengenes vedkommende og det fyldte 11 år for pigernes vedkommende er der foretaget en ny vurdering fordi vurderingen af håndrodsknoglerne var behæftet med visse vanskeligheder

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I *kapitlerne VII–VIII* har man søgt at vurdere i hvor høj grad skeletalderen kan anvendes som mål for den biologiske udvikling, idet man har sammenholdt den med andre udviklingskriterier som højde, indtræden af menarche, mamma og pubesudvikling m. m..

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I *kapitel VII* sammenlignes forskellige norske, svenske og amerikanske højdetabeller med resultatet af nærværende undersøgelses højdemålinger Børnene i nærværende undersøgelse er målt i højdeår ca. et halvt år retarderet i forhold til børnene i Brush Foundation materialet, som ligger til grund for Greulich & Pyle's atlas. Der er påvist signifikant større korrelation mellem højde og skeletalder end mellem højde og kronolgisk alder

I *kapitel VIII* refereres tidligere undersøgelser over menarchealderen Det fremgår tydeligt at menarchen ind

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Man har ikke kunnet påvise, at det havde indflydelse på børnenes udvikling, om moderen havde udeerhverv eller ej.

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BY BENGT ROBERTSON

ALMQVIST & WIKSELLS BOKTRYCKERI AB UPPSALA

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by

BENGT ROBERTSON

STOCKHOLM 1968

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III. ROBERTSON B. The neonatal intrapulmonary arterial pattern in transposition of the great arteries. A microangiographic and histological study. *Virchows Arch Path Anat* 344: 213—229.

IV. ROBERTSON B. The intrapulmonary arterial pattern in infants with transposition of the great arteries associated with interventricular septum defect. A microangiographic and histological study. *Virchows Arch Path Anat* 344: 230—242.

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Tryckeri Balder AB Stockholm 1963

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I ROBERTSON B The normal intrapulmonary arterial pattern of the human late fetal and neonatal lung. A microangiographic and histologic study. *Acta Paediat Scand* 56 249—264, 1967

II ROBERTSON, B The normal intrapulmonary arterial pattern in infancy and early childhood. A microangiographic and histological study. *Acta Path Microbiol Scand* 71 481—501 1967

III. ROBERTSON B The neonatal intrapulmonary arterial pattern in transposition of the great arteries. A microangiographic and histological study. *Virchows Arch Path Anat* 344 213—229

IV ROBERTSON B The intrapulmonary arterial pattern in infants with transposition of the great arteries associated with interventricular septum defect. A microangiographic and histological study. *Virchows Arch Path Anat* 344 230—242.

Brief preliminary reports dealing with various phases of the work have been published in the following papers

ROBERTSON B Microangiographic studies of the lung in transposition of the great arteries. Proceedings of the Fourteenth Northern Pediatric Congress. *Acta Paediat Scand* Suppl. 159 84—85 1964.

ROBERTSON B Arterial bronchopulmonary anastomoses in the human neonatal lung. *Conference on Pulmonary Circulation, Oslo 1965* Ed. Carsten Müller Universitetsforlaget, Oslo, 1966, pp 133—136.

ROBERTSON B The bronchial artery in the fetal and neonatal lung. *Acta Paediat Scand* 56 119 1967

CONTENTS

CONTENTS

INTRODUCTION

This work was originally started with the purpose of investigating the incidence of arterial bronchopulmonary anastomoses in the normal human infant lung and in congenital heart disease. These anastomoses are of particular interest in cardiovascular malformations, since the anastomoses — at least in conditions with reduced pulmonary arterial flow — serve as a shunt between the systemic and pulmonary circulations (10 22, 28, 34, 50 51).

During the course of the study it became evident, however that the significance of the arterial bronchopulmonary anastomoses could be better understood if the study was extended to include other aberrations from the basic arterial pattern of the lung, such as pulmobronchial arteries and bronchopulmonary arteries.

Transposition of the great arteries was the first type of congenital heart disease chosen for investigation. This malformation is incompatible with life unless the anatomic conditions permit mixing of the systemic and pulmonary blood flow In the absence of anomalies of venous return and cardiac septal defects, these infants largely depend upon the shunting capacities of the foramen ovale and the ductus arteriosus. This part of the study was undertaken to find out *a)* whether isolated transposition is associated with any particular type of intrapulmonary arterial pattern which might offer an auxiliary shunt, or crossing-over between the systemic and pulmonary circulations otherwise connected in parallell and *b)* whether, in transposition, the intrapulmonary arterial pattern is influenced by the presence of interventricular septum defect.

Arterial Bronchopulmonary Anastomoses, Pulmobronchial Arteries and Bronchial-Artery Supply of the Pulmonary Parenchyma in Infancy and Childhood

Normal. The discovery of the arterial bronchopulmonary anastomoses has been attributed to Ruysch, who on the basis of injection studies gave the following description, in 1696

"Variis autem locis haec arteria bronchialis anastomosibus associatur ramusculis minutissimis arteriae pulmonalis. Repleta enim arteria pulmonali ceracea materia illico quoque repleti conspiciuntur ramuli arteriae bronchialis nullusque dubito, quin hoc vice versa quoque fiat, quamvis id nunquam tentarim* (45)

Since the original description there has been a great deal of controversy concerning the incidence of arterial bronchopulmonary anastomoses in the normal human lung. Many workers claim to have demonstrated their existence (20, 23 4, 27—31 52) others have denied the normal occurrence of any precapillary communication between the bronchial and pulmonary arterial systems (7 13, 42, 47 51 58) The methods employed in these studies of the arterial bronchopulmonary anastomoses have been the corrosion cast technique (20 24, 29) angiography (7 13 20, 29 42, 47 58) microangiography (30, 31 51) and serial sectioning (13 28 29 52) Most of these studies were probably performed on adult material the ages of the subjects were usually not given.

The first report with special reference to the developing lung was presented by Küttner in 1878 (26) Using injection and corrosion cast techniques, he studied the human pulmonary arterial pattern in the late fetal period and in the newborn. He reported the frequent occurrence of subpleural anastomoses between bronchial and pulmonary arteries but does not seem to have noticed any intrapulmonary arterial anastomoses. Küttner observed, however, that branches from the pulmonary artery contribute to the arterial supply of the bronchi. He also recognized that the bronchial arteries of the fetus and newborn supply small areas of the pulmonary parenchyma proper in addition to the bronchial structures

Using injection techniques and dissection, Zuckerkandl in 1883 (59) confirmed the findings of Küttner concerning the subpleural anastomoses between bronchial and pulmonary arteries Zuckerkandl, however also demonstrated intrapulmonary ("tief liegenden") arterial bronchopulmonary anastomoses of the end-to-side and the end-to-end type. He further includes in the concept of anastomoses the *rami bronchiales arteriae pulmonalis* i.e. branches from the pulmonary artery supplying the bronchial tree. These various types of anastomoses, ac

* In many places the bronchial artery is connected as anastomoses with small branches of the pulmonary artery For when the pulmonary artery is injected with wax, branches of the bronchial artery are also filled no doubt the opposite (filling of the pulmonary artery by injection of the bronchial arteries) would also take place, although I have not yet tried so.

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cording to Zuckerkandl, may reach a diameter of 500 μ in the human lung

Konaschko in 1926 (25) made corrosion casts of the pulmonary and bronchial arteries of human infants newborn to 1 year of age. Without stating their frequency Konaschko reported the occurrence of intrapulmonary ("tiefliegenden") arterial bronchopulmonary anastomoses of the end to-side and of the end to-end type. He also observed subpleural end to-end anastomoses between bronchial and pulmonary arteries. These anastomoses were found particularly at the mediastinal aspect of the lung, less frequently in the diaphragmatic and costal areas The diameter of the subpleural anastomoses, according to Konaschko varies between 0 3 and 1 mm. Konaschko also recognized that the bronchial arteries normally supply small areas of the pulmonary parenchyma proper

Arterial bronchopulmonary anastomoses were found in the lungs of newborn and older infants by Verloop in 1948 (53) and by Weibel, in 1959 (57) who both used serial sectioning, and by Marchand Gilroy & Wilson, in 1950 (37) who used the corrosion cast technique and angiography these observations were, however based on very small series. Verloop described deep-lying and superficial anastomoses, the former being the more frequent, but remarked that these anastomoses are rare in the human neonatal lung (53) According to Weibel, the arterial bronchopulmonary anastomoses do not occur regularly but haphazardly and infrequently in the human neonatal lung (57) Marchand, Gilroy & Wilson were unable to demonstrate such anastomoses by the corrosion cast technique in the human neonatal lung Anastomoses were found, however with the same technique in the lungs of a two-year-old human infant, who had died of meningitis and whose lungs were considered normal In angiographic studies by the same workers on lung specimens from newborn infants, contrast medium passed from the bronchial to the pulmonary arteries indicating precapillary communications between the two arterial systems of the lung (37)

Tobin, in 1952 (50) made injection studies of the arterial pattern of human lungs from subjects of varying age. Arterial bronchopulmonary anastomoses were found though not consistently in the lungs of newborn and older infants, but their relative frequencies in various age groups were not analyzed

Liebow et. al. (1959) concluded from corrosion casts of the pulmonary vasculature that "localized congenital communications between the systemic and pulmonary arteries in the absence of heart disease occur with extreme rarity (33)

No arterial bronchopulmonary anastomoses were reported by Marini & Camarri, who employed serial sectioning in their study on the vasculature of the human fetal lung (38 39)

Wagenvoort, Heath & Edwards, in 1964, stated that arterial bronchopulmonary anastomoses occur "relatively often and close together in the lungs of fetuses and infants After the age of two years according to the same investigators, these anastomoses are rare in the absence of cardiac or pulmonary disease (54)

In a recent study on the vasculature of human "perinatal lungs Wagenvoort & Wagenvoort using serial sectioning demonstrated only occasional arterial bronchopulmonary anastomoses More frequent than the anastomoses were pulmobronchial

arteries (bronchial arteries originating from pulmonary arteries) Focal bronchial artery supply of the pulmonary parenchyma proper was demonstrated in most specimens from the late fetal and immediate neonatal period. This feature was particularly prominent in immature subjects and was not encountered in infants older than 6 weeks (55 56)

Transposition of the g eat arteries Previous structural investigations on the vasculature of the infant lung in transposition of the great arteries have largely been concerned with the effects of pulmonary hypertension on the pulmonary arterial bed. Medial hypertrophy in muscular pulmonary arteries, intimal proliferation, thrombotic and plexiform lesions have been reported to occur from the age of 1—2 months, though particularly in cases with coexisting interventricular septum defect (18, 19 43, 54) Increased bronchial-artery supply of the lungs, however has been reported in infants and older subjects with transposition of the great arteries (1 2, 10—12, 14, 15 17 19 28) but the intrapulmonary course of the bronchial arteries was not analyzed in detail, nor were the findings correlated to the presence of associated cardiac defects.

Microangiographic technique has not previously been applied to the study of the pulmonary vasculature in transposition of the great arteries.

MATERIAL

The material consisted of autopsy lung specimens from

I) 37 neonatal (immature, premature and full-term) infants without evidence of cardiovascular malformation or abnormal pulmonary histiogenesis,

II) 15 infants, ranging in age from 3 weeks to 4 years and 7 months, all without evidence of malformations involving the respiratory or cardiovascular systems and without evidence of chronic pulmonary disease,

III) 10 infants, ranging in age from 5 hours to 1 month and 24 days with transposition of the great arteries as an isolated cardiovascular malformation and

IV) 7 infants, ranging in age from 4 days to 4 months and 27 days, with transposition of the great arteries associated with interventricular septum defect.

In the majority of the subjects, including all subjects in series III and IV both lungs were available for microangiographic examination In the remaining subjects only one lung was available, either because of diagnostic procedures or because of failure of injection. In series I which originally consisted of 41 subjects, 4 had to be excluded because of incomplete filling of the lung specimen or extensive vascular ruptures.

The series of normal neonatal autopsy subjects (I) was selected, in order to get a fairly uniform representation of different gestational age groups. The remaining series (II—IV) were collected consecutively

A survey of the material is given in Table 1

Table 1 *Survey of the material*

Diagnosis, age	Number of subjects	Lungs injected		Number of stereoscopic pairs of microangiograms per subject, mean	Number of blocks serially sectioned per subject, mean
		one	both		
Normal Late fetal and neonatal period Birth weight range 450—4250 g	37	7	30	6	13
Normal Infancy and early childhood	15	5	10	13	12
Transposition of the great arteries. Early infancy	10		10	11	9
Transposition of the great arteries + interventricular septum defect. Early infancy	7		7	9	5
Total	69	12	57		

The pulmonary or bronchial arteries were injected with 7.5 per cent tap water (pH 6.4) suspension of fine barium sulphate (Micropaque ® Damancy & Co). This contrast medium, which has a particle diameter of 5—6 μ (21), reaches the capillary bed of the lung.

For the injection of the *pulmonary arterial system* one or both lungs (including the bronchi and the trachea) were removed at autopsy and separated from the heart. The injection was made into the pulmonary arteries of each lung or into the pulmonary trunk after ligation of the ductus arteriosus — when not anatomically closed. The pulmonary veins were left open. The injection pressure was recorded and kept around 60 mm Hg (40—80 mm Hg) non-pulsatile, in specimens from normal fetuses and infants (I, II). In specimens from both groups of infants with transposition (III, IV) the pulmonary arteries were injected at a pressure of about 100 mm Hg (80—120 mm Hg). The lungs were unexpanded and in atmospheric conditions during the injection procedure. Irregular capillary filling in subpleural pulmonary lobules was usually visible within the first minute of injection. Capillary filling rapidly increased as did the volume of the injected lung. After a few minutes, the lung appeared to be more or less saturated with contrast the consumption of contrast decreased, but did not cease altogether. I most instances, a slight leakage of contrast through the open pulmonary veins was observed during the injection.

For the filling of the *bronchial arterial system* the thoracic viscera were removed *en bloc* without opening the oesophagus, the trachea or the bronchi. The heart was removed and the following arteries were ligated the ascending aorta, the pulmonary trunk, the ductus arteriosus (when not anatomically closed) the common carotid, subclavian and intercostal arteries. The pulmonary veins were left open. A cannula was tied into the thoracic aorta with its tip slightly above the level of the diaphragm. I jection was made at a pressure of about 100 mm Hg (80—120 mm Hg) throughout the series. Contrast leakage through small mediastinal arteries opened when removing the specimen was prevented by clamping and ligation and could, as a rule, be reduced to a minimum. Filling of pleural branches of the bronchial arteries was usually visible within a few minutes at the mediastinal aspect of the lung and at the interlobar fissures. In some specimens incomplete capillary filling of the pulmonary parenchyma, visible from the pleural surface, indicated either transmission of contrast from one arterial system to the other or the presence of direct systemic-artery supply of the pulmonary parenchyma. A light flow from the open pulmonary veins was observed in some specimens.

A few lung specimens from infants with transposition were double-injected first *via* the bronchial arteries and thereafter *via* the pulmonary arteries (III, IV).

The injection time was generally at least 30 minutes (60 minutes in the double-injected specimens).

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The injection time was generally at least 30 minutes (60 minutes in the double-injected specimens).

After injection, the filling was checked in survey radiograms of the entire specimen. The injected lungs were fixed in neutral formalin for at least 4 days. Frontal slices of the lungs 2—3 mm thick, were then radiographed and representative specimens were taken from all lobes of the lungs including the hilus. Regions with evidence of transmission of contrast from one arterial system to the other were particularly looked for and selected for microangiography. The selected specimens were embedded in a mixture of 4/5 Histowax® (Matheson Coleman & Bell) and 1/5 yellow bees wax. This type of embedding gives to the specimen a consistency suitable for the subsequent cutting in slices 1000—2000 μ thick.

In the following microangiographic procedure, the exposure was made on Kodak Maximum Resolution Plates, which have a resolution better than 1000 lines per mm. A Matchlett OEG 50 X-ray tube was used (40 kV 8 mA) with a focus-to-film distance of 90 cm and an exposure time of 3 hours. The specimen was in contact with the film during the exposure. A stereo-pair of microangiograms was produced from each block by moving the specimen laterally on the base plate between the exposures. A displacement of the specimen of 15 cm, corresponding to an angle of 9° between the two exposures, was found to give an acceptable threedimensional image. An average of 6—13 pairs of microangiograms measuring about 3×4—6 cm were produced in each subject (Table 1).

The microangiograms were scrutinized in a stereo-microscope and areas of particular interest were cut out from the blocks and re-embedded in paraffin for histologic examination. Serial sections were cut from all areas with evidence of arterial broncho-pulmonary anastomoses or pulmobronchial arteries in the microangiograms, and from other areas with an unusual appearance. The histologic sections, 6—7 μ thick, were stained with Verhoeff's or Weigert's elastic tissue stain and counterstained with van Gieson stain. An average of 5—13 blocks were serially sectioned in each subject (Table 1).

Comment

The injection pressure levels used in this study were chosen according to the following principles:

a) they should approximate the intra-vitam levels, and

b) they should be kept constant throughout the series in order to permit a comparison of vascular diameters in corresponding areas of the injected specimens.

The simultaneous fulfillment of both these principles is obviously difficult in a material consisting of immature, premature and full-term fetuses, neonatal and older normal infants and children as well as neonatal and older infants with transposition of the great arteries. The pressure of 60 mm Hg (40—80 mm Hg) corresponds rather well to the normal pressure in the pulmonary artery in the fetal and immediate neonatal period, but it is obviously too high for older infants and children. The pressure of 100 mm Hg (80—120 mm Hg) used for the injection of the pulmonary arterial system in transposition of the great arteries was chosen to match the pulmonary hypertension regularly present in these infants (49). The same pressure of 100 mm Hg (80—120 mm Hg) used throughout the series for the injection of the bronchial arterial system approximates the intra-vitam level in normal infancy and childhood as

well as in transposition of the great arteries. The pressure, however is too high for the late fetal period. Consequently the choice of injection pressure levels in the present study is the result of a compromise between the two principles outlined above.

In the initial phase of the study a longer injection time was used ($\leq 2\frac{1}{2}$ hours) but since it became evident that the injection time could be considerably reduced without altering the degree of filling of the specimens (as checked in survey radiograms and in the microangiograms) the injection time was settled at 30 minutes. In a few fetal specimens the injection had to be discontinued earlier because of vascular ruptures. Shorter injection periods were not tested.

The microangiographic technique was introduced by Bohatyrtschuk (8) and later developed by Barclay (3 4) Bellman and Engström (5 6) made an analysis of the technique, examining in particular the factors that influence the quality of the radiogram, such as the type of film, contrast medium and X-ray equipment. The advantages of the stereo-microangiographic technique compared with other forms of injection methods, such as stain injection, corrosion cast technique and regular angiography were pointed out by Ljungqvist in his microangiographic study of the arterial pattern of the human kidney (35) Microangiography seems to be the best method for the purpose of the present study since it permits subsequent histologic examination of the specimens by serial sectioning — the only reliable way of morphologically demonstrating the existence of vascular anastomoses (48) With the combination of microangiographic and histologic techniques, the time-consuming procedure of "blind" serial sectioning is avoided.

Overlapping phenomena constitute an important challenge to the recognition of vascular communications in plain microangiograms. This difficulty is considerably reduced by the stereo-microangiographic technique, by which — as a rule — the vessels can be "separated" from one another and their spatial course can be followed. The distortion of the vascular pattern in the microangiographic image, due to varying vessel-to-film distance, can be disregarded owing to the wide focus-to-film distance (90 cm) The same holds for the small distortion of the vascular pattern due to the lateral movement of the specimen between the two exposures in the production of a stereoscopic pair of microangiograms. The re-embedding and subsequent histologic sectioning of selected areas of the radiographed blocks generally resulted in a slight shrinkage of the specimens with some further distortion of the vascular pattern, as compared to the microangiographic image. The injected vessels, however, could be recognized without difficulty in the histologic slides, and their course in the microangiograms could easily be related to the various levels in serial sections.

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RESULTS

Pulmonary arterial system

Basic pattern

Normal The branches of the pulmonary artery generally follow those of the bronchi The "medullary (circumhilar) zone of the lung, however is also normally supplied by numerous muscular lobular arteries arising more or less perpendicularly from the elastic pulmonary arteries These "abrupt branches are much narrower than their parent vessel and they are not accompanied by a bronchus at their point of origin After entering an adjacent lobulus, some of these branches can be seen to join an intralobular bronchus of corresponding size (I II)

A few pulmonary arterioles leave their lobules to supply either septal tissue or the pleura. These vessels run at the costal, basal and mediastinal aspects of the lung and at the interlobar fissures. Their diameter ranges from 25 to 75 μ in the late fetal — neonatal lung (I) and from 25 to 250 μ in infancy and early childhood (II) A few of these vessels form arterial bronchopulmonary anastomoses (see below)

Occasionally a pulmonary arteriole or a muscular pulmonary artery traverses the interlobular septum to ramify in an adjacent lobulus. This feature was encountered in a few specimens from normal late fetal — neonatal lungs (I) and in one specimen from a normal infant, age two year and eight months (II)

Transposition of the great arteries Deviation from the normal intrapulmonary arterial pattern was observed in all pulmonary artery injected lung specimens from infants with *isolated transposition* i.e. in six subjects. Two fairly distinct types of peripheral arterial pattern were recognized in the microangiograms and were arbitrarily denoted as Type I and Type II

Type I present in three subjects, is characterized by a rapid decrease in the diameter of the lobular pulmonary arteries at a level corresponding to the zone of transition of mural structure from predominantly elastic to predominantly muscular Peripherally to the funnel shaped narrowing, the pulmonary arteries branch into bundles of small muscular arteries of about equal size, some of which even slightly wider than their parent artery Many of these branches display focal narrowing through intimal cushions of endothelial and smooth-muscle cells.

In Type II present in the other three subjects there is a more gradual decrease in the diameter of the pulmonary arteries towards the periphery of the lung Deviation from the normal pattern is seen predominantly in the form of increased tortuosity of intralobular pulmonary arteries.

Abrupt muscular branches from elastic pulmonary arteries were about as frequent as in specimens from normal fetuses and infants and their frequency was unrelated to the Type I or the Type II patterns Particularly in specimens with Type I pattern many of the abrupt branches are narrowed shortly after their point of origin by intimal

cushions of endothelial and smooth-muscle cells. In three of the subjects with isolated transposition, the subdivisions of many of the abrupt branches from octopus-like bundles in one of these subjects the abnormal abrupt branches give rise to several pulmobronchial arteries (see below)

In two infants with isolated transposition (ages 10 days and 21 days, bronchial-artery injected specimens) *obliterated* muscular pulmonary arteries were encountered in areas also supplied by "bronchopulmonary arteries (see below) indicating that the arterial supply of these areas had been taken over by the bronchial arterial system.

A few pulmonary arterioles leave their lobules to supply either septal tissue or the pleura or to anastomose end-to-end with septal or pleural branches of the bronchial arteries (see below) The diameter of these "penetrating pulmonary arterioles ranges up to 125 μ (III)

In the series of seven infants with *transposition associated with interventricular septum d fect* the Type I of intralobular arterial pattern was not encountered. The microangiographic pattern of the pulmonary arterial system was essentially normal in two subjects. In three subjects there was increased tortuosity of intralobular pulmonary arteries, corresponding to the abovementioned Type II pattern. In the two remaining subjects the injection had been made into the bronchial arteries and a microangiographic analysis of the pulmonary arterial pattern was not possible.

Abrupt muscular branches from elastic pulmonary arteries were about as frequent and of the same type as in the normal infant lung

In one subject, a few pleural branches of the pulmonary artery were demonstrated at the costal and mediastinal aspects of the lung Their diameter ranges from 35 to 50 μ (IV)

Comment

The findings concerning the normal basic pattern of the pulmonary arterial system essentially agree with earlier observations. The "Type I pattern of intralobular pulmonary arteries, however demonstrated in infants with isolated transposition, does not seem to have been recognized previously The rapid, funnel-shaped decrease in the diameter of the intralobular pulmonary arteries in combination with the cellular intimal cushions of these arteries suggest a higher vascular resistance than normal or in the "Type II" pattern. This could be related to low survival time of individuals with Type I pattern compared with those with Type II pattern (III)

Tortuosity of intralobular pulmonary arteries — a prominent feature of the Type II pattern — is obviously not specifically related to transposition of the great arteries, since it has been observed in post-mortem angiograms from cases of pulmonary hypertension secondary to other forms of congenital heart disease (16, 46)

Pulmobronchial arteries

The term pulmobronchial arteries was recently suggested by Wagenvoort & Wagenvoort (55 56) to denote intrapulmonary bronchial arteries originating as branches of the pulmonary artery These structures, which appear to substitute for the "ordinary bronchial arteries along a few bronchi, were previously referred to as *rami pulmobronchiales* (9 23, 24) or *rami bronchiales arteriae pulmonalis* (59)

RESULTS

Pulmonary arterial system

Basic pattern

Normal The branches of the pulmonary artery generally follow those of the bronchi. The "medullary (circumlobular) zone of the lung, however is also normally supplied by numerous muscular lobular arteries arising more or less perpendicularly from the elastic pulmonary arteries. These "abrupt branches are much narrower than their parent vessel and they are not accompanied by a bronchus at their point of origin. After entering an adjacent lobulus, some of these branches can be seen to join an intralobular bronchus of corresponding size (I II)

A few pulmonary arterioles leave their lobules to supply either septal tissue or the pleura. These vessels run at the costal basal and mediastinal aspects of the lung and at the interlobar fissures. Their diameter ranges from 25 to 75 μ in the late fetal — neonatal lung (I) and from 25 to 250 μ in infancy and early childhood (II) A few of these vessels form arterial bronchopulmonary anastomoses (see below)

Occasionally a pulmonary arteriole or a muscular pulmonary artery traverses the interlobular septum to ramify in an adjacent lobulus This feature was encountered in a few specimens from normal late fetal — neonatal lungs (I) and in one specimen from a normal infant, age two year and eight months (II)

Transposition of the great arteries Deviation from the normal intrapulmonary arterial pattern was observed in all pulmonary artery injected lung specimens from infants with *isolated transposition* i.e in six subjects Two fairly distinct types of peripheral arterial pattern were recognized in the microangiograms and were arbitrarily denoted as Type I and Type II

Type I present in three subjects, is characterized by a rapid decrease in the diameter of the lobular pulmonary arteries at a level corresponding to the zone of transition of mural structure from predominantly elastic to predominantly muscular Peripherally to the funnel shaped narrowing the pulmonary arteries branch into bundles of small muscular arteries of about equal size, some of which even slightly wider than their parent artery Many of these branches display focal narrowing through intimal cushions of endothelial and smooth-muscle cells.

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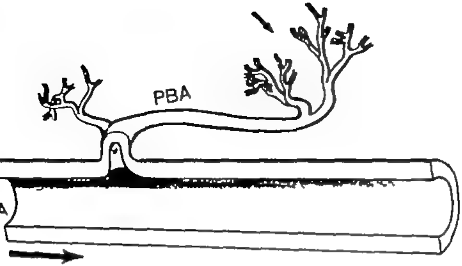
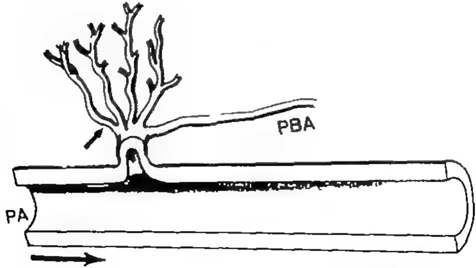


C Abnormal pulmobronchial artery (PBA) with *arrayed* ramifications to the pulmonary parenchyma proper (*small arrow*) Isolated transposition of the great arteries



D Abnormal pulmobronchial artery (PBA) originating as part of octopus-like ramifications (*small arrow*) of abrupt branch of the pulmonary artery (PA) Isolated transposition of the great arteries.

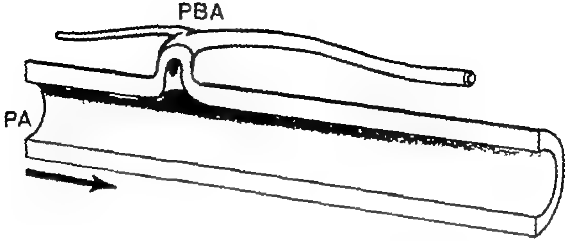
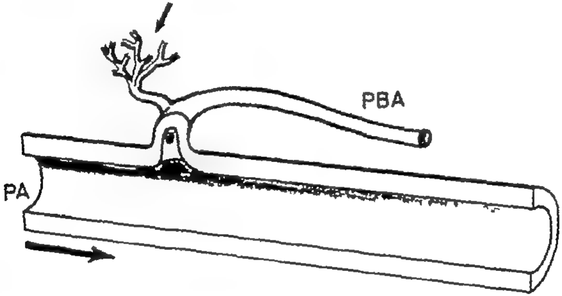


Fig 1 Diagrams showing various patterns of pulmobronchial arteries. Direction of flow in the pulmonary artery (PA) is indicated by *big arrows*

A. Normal pulmobronchial artery (PBA) with concurrent and recurrent branches.



B. Normal pulmobronchial artery (PBA) with concurrent branch and small ramifications to the pulmonary parenchyma proper (*small arrow*)

Normal Pulmobronchial arteries were demonstrated in small numbers in 9 of 37 subjects (24 per cent) in the study of the late fetal and neonatal lung Their diameter at their points of origin ranges from 25 to 100 μ (I) In the study of the pulmonary vasculature in infancy and early childhood, pulmobronchial arteries were demonstrated in 8 of 15 subjects (53 per cent) They are few in number and their diameter ranges from 50 to 330 μ (II)

After leaving their parent pulmonary artery the pulmobronchial arteries generally turn distally along the neighboring bronchus but they also send recurrent branches along the same bronchus (Fig 1 A) Small rami

the origin of an arterial vessel in the bronchial wall. Consequently there is a degree of uncertainty in the classification and counting of these structures, and the absolute figures given above for their incidence should be regarded as approximate. The relative frequencies, however are unlikely to have been systematically influenced.

The diameter of the pulmobronchial arteries were measured on injected vessels, which were often distended with contrast. Furthermore, the injection pressure was not uniform throughout the series (cf p. 15) The diameter values therefore cannot be regarded as a reliable index of functional capacity The findings in the present study concerning the size of the pulmobronchial arteries are, however, similar to the *findings* of Wagenvoort & Wagenvoort in their recent histological study on the vasculature of the human perinatal lung (56)

Pulmobronchial arteries with abnormal terminal ramifications in the pulmonary parenchyma — as demonstrated in isolated transposition — are sometimes *difficult to* distinguish from ordinary abrupt branches crossing the bronchial wall. An artery was classified as pulmobronchial, however, when it penetrated the cartilage level of the bronchial wall.

Bronchial arterial system

Basic pattern

Normal The bronchial arteries of the normal lung generally accompany the bronchi. Apart from their ramifications in the bronchial walls proper, they form the *vasa vasorum* of the major pulmonary vessels. They also supply septal tissue near the hilus as well as lymph nodes and peribronchial nerves. Pleural branches of the bronchial arteries occur regularly particularly near the hilus and at the interlobar fissures (I, II)

The inner diameter of the main bronchial arteries in the hilus of the late fetal and neonatal lung increases with fetal age and ranges from 125 to 300 μ (I) In infancy and early childhood (i.e. up to the age of four years and seven months) the diameter of the main bronchial arteries in the hilus of the lung ranges from 350 to 600 μ and does not seem to increase with age (II)

From the age of ten weeks, longitudinal intimal muscle cells are normally present in the bronchial arterial system, but the bronchial arteries are not uniformly involved. Particularly affected are branches forming the *vasa vasorum* of the main pulmonary vessels and those participating in arterial bronchopulmonary anastomoses (see below) Even among the "ordinary bronchial arteries, there is a variation within the same specimen, but as a rule the "Sperr artery structure of intrapulmonary and pleural bronchial arteries becomes more prominent with age. From the age of one year and four months some bronchial artery derived *vasa vasorum* of the pulmonary artery are completely obliterated by smooth muscle cells (II)

Transposition of the great arteries In transposition, with or without interventricular septum defect, the basic pattern of the bronchial arterial system does not deviate from the normal, i.e. the bronchial arteries largely follow the course of the bronchi, supplying the bronchial structures and lymph nodes. Pleural branches occur, as normally at the mediastinal aspect of the lung and at the interlobar fissures (III, IV)

fications to adjacent alveolar walls are occasionally observed These ramifications originate *proximal* to the point where the artery joins the bronchial wall (Fig 1 B) (I II)

The majority of the pulmobronchial arteries originate from elastic pulmonary arteries but occasionally they arise from intralobular pulmonary arterioles leaving their lobulus to join an adjacent prelobular bronchus This latter feature was observed only in the study of infancy and early childhood (II)

The mural structure of the pulmobronchial arteries, after they join the bronchial wall, cannot be distinguished from that of the ordinary bronchial arteries Like the latter they often accompany the peribronchial nerves. From the age of 11 weeks, they occasionally have a thin intimal layer of smooth muscle cells ("Sperr artery structure [24]) (I II)

Transposition of the great arteries In neonatal subjects with *isolated transposition* pulmobronchial arteries were demonstrated in three subjects (30 per cent) Their diameter at the point of origin ranges from 50 to 275 μ. They have the same mural structure as those of the normal neonatal lung

Divergence from the normal pattern was observed in the following aspects

a) Many of the pulmobronchial arteries deviated from the bronchial walls in their terminal course to ramify into alveolar capillaries The diameter of these deviating branches ranges up to 100 μ (Fig 1 C)

b) In one subject the pulmobronchial arteries were particularly frequent and some of them arose as part of octopus like ramifications of abrupt muscular branches from elastic pulmonary arteries (Fig 1 D) (III)

In the series of seven infants with *transposition associated with interventricular septum defect* a few pulmobronchial arteries were demonstrated in two subjects. Their diameter ranges from 75 to 200 μ and their course does not, as a rule, deviate from the normal pattern An exception is formed in one specimen by the presence of an anastomosis of side to-side type (diameter 75 μ) between a pulmobronchial artery and an adjacent "ordinary bronchial artery The mural structure of the pulmobronchial arteries is essentially the same as in the normal infant lung "Sperr artery structure of pulmobronchial arteries, however was not encountered in this part of the series (IV)

Comment

The microangiographic technique offers a fairly complete screening of the arterial systems of the lung but the points of origin of pulmobronchial arteries are sometimes hidden by close overlapping or by being present near or at the borderline between two slices of lung tissue A further source of error is the resemblance between pulmobronchial arteries with recurrent branches and arterial bronchopulmonary anastomoses. A pulmobronchial artery with recurrent branches can be distinguished from a true anastomosis, however since the recurrent branch gradually decreases in size towards the hilus whereas the opposite is true of a bronchial artery proximal to an anastomosis. This distinction may be very difficult even impossible, if the recurrent branch of a presumed pulmobronchial artery can be followed for only a short distance in the microangiograms or in the serial sections and its diameter remains constant in its visible portion. The wall structure *per se* is no clue to

the origin of an arterial vessel in the bronchial wall. Consequently there is a degree of uncertainty in the classification and counting of these structures and the absolute figures given above for their incidence should be regarded as approximate. The relative frequencies, however are unlikely to have been systematically influenced.

The diameter of the pulmobronchial arteries were measured on injected vessels, which were often distended with contrast. Furthermore, the injection pressure was not uniform throughout the series (cf p 13) The diameter values therefore cannot be regarded as a reliable index of functional capacity The findings in the present study concerning the size of the pulmobronchial arteries are, however similar to the findings of Wagenvoort & Wagenvoort in their recent histological study on the vasculature of the human perinatal lung (56)

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The inner diameter of the main bronchial arteries in the hilus of the late fetal and neonatal lung increases with fetal age and ranges from 125 to 300 μ (I) In infancy and early childhood (i.e. up to the age of four years and seven months) the diameter of the main bronchial arteries in the hilus of the lung ranges from 350 to 600 μ and does not seem to increase with age (II)

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In neonatal instances of *isolated transposition* the diameter range of the main bronchial arteries in the hilus of the lung *is increased to 375—1200 μ. In two subjects* with particularly wide and tortuous bronchial arteries, enlargement of the aortic orifices of the bronchial arteries was recorded at autopsy (III).

In infants with *transposition associated with interventricular septum defect* the diameter of the main bronchial arteries in the *hilus of the lung ranges from 175 to 475 μ*, i.e. within normal limits (IV). In neither *of the two series of infants with transposition* did the bronchial arteries display the mural structure of "Sperr"-arteries (III, IV).

Comment

The findings concerning the normal basic pattern of the bronchial arterial system are essentially in agreement with earlier observations by others. The "Sperr" artery structure of bronchial arteries, however, has not previously been recognized before the age of seven months (40). The functional claim on the bronchial arteries as oxygen carriers to the bronchial and peribronchial structures is most probably greater in the intrauterine state than in the postnatal *breathing lung*. Apart from the fact that the bronchial surface of the postnatal lung is in direct contact with air, the oxygen supply of the bronchial structures can — *at least in part* — be taken over by the pulmonary veins that drain *into the peribronchial* venous plexuses. The gradual development of "Sperr" artery structure in the bronchial arteries of the human postnatal lung can therefore be regarded as a process of involution or adaptation to extrauterine type of circulation. This theory, suggested by Verloop (53) and by Preto Parvis (44), is further supported by the findings of the present study concerning the size of the main bronchial arteries in the hilus of the lung. Whereas the diameter of these arteries increases with fetal age, it remains fairly constant during the first few years of postnatal life (II).

The increased size of the main bronchial arteries in cases of isolated transposition is obviously related to the extensive bronchial artery supply of the pulmonary parenchyma proper (III) (se below).

Bronchopulmonary arteries

The term "bronchopulmonary arteries", *which was recently suggested by Wagenvoort & Wagenvoort* (55, 56), indicates branches of the bronchial arteries which enter the pulmonary parenchyma proper to ramify into capillaries of alveolar walls.

Normal. Bronchopulmonary arteries were observed in all but one of the aorta injected specimens in the series of normal late fetal and neonatal lungs. Their diameter ranges up to 120 μ. They are particularly common in the "medullary" zone of the lung and are sometimes surrounded by a narrow sleeve of lymphoid tissue at their point of *entrance into the pulmonary parenchyma*. In places they substitute for the pulmonary artery along terminal bronchioles, and here their wall structure cannot be distinguished *from that of peripheral pulmonary arterioles* (I).

In the series of 15 subjects from infancy and early childhood, bronchopulmonary arteries (diameter range ≤ 200 μ) were demonstrated in 8 subjects varying in age from four weeks to four years and seven months. At the age of four weeks, the bronchopulmonary arteries have about the same frequency and extent *as in the normal neo-*

natal lung. From the age of six months, these arteries are only rarely encountered in the microangiograms. Particularly near their points of origin, some of the broncho-pulmonary arteries are thickwalled and narrow occasionally even obliterated by intimal layers of smooth muscle cells. This "Sperr" artery structure of bronchopulmonary arteries was not observed until the age of seven months (II)

In a few instances a pulmobronchial artery originates not far from the point where a bronchopulmonary artery deviates from the bronchial wall, indicating that the former substitutes for the latter by taking over the arterial supply of the bronchial wall. This feature was observed in the series of late fetal and neonatal lungs (I)

In places, contrast medium appeared to have passed from bronchopulmonary arteries to adjacent branches of the pulmonary artery though a common capillary network (I, II)

When present, the direct bronchial-artery supply of the pulmonary parenchyma (as bronchopulmonary arteries) consistently involved only a minute part of the normal late fetal and postnatal infant lung (I, II)

Transposition of the great arteries In isolated transposition there is prominent increase in the bronchial-artery supply of the pulmonary parenchyma. Although evident already in the neonatal period, this increase is still more pronounced in infants who survive the immediate neonatal period The bronchopulmonary arteries are numerous and they are derived from intrapulmonary as well as pleural branches of the bronchial arteries. Intrapulmonary bronchopulmonary arteries supply a large portion of the "medullary" zone of the lung The inner diameter of the bronchopulmonary arteries, at their points of entrance into the pulmonary parenchyma, ranges up to 200 μ. Their mural structure is the same as in the normal neonatal lung (III)

In the series of 7 infants with *transposition associated with interventricular septum defect* bronchopulmonary arteries were demonstrated in all aorta injected specimens and in one of the pulmonary artery injected specimens. Their number is within normal limits in three subjects and moderately increased in two subjects. Their diameter ranges up to 125 μ. As in the series of infants with isolated transposition, the majority of the bronchopulmonary arteries are derived from intrapulmonary bronchial arteries in the "medullary" zone of the lung, but a few small bronchopulmonary arteries (diameter range up to 50 μ) originate from pleural branches of the bronchial arteries. The mural structure of the bronchopulmonary arteries does not differ from the normal.

Transmission of contrast from bronchopulmonary arteries to adjacent branches of the pulmonary artery (or *vice versa*) indicating a common capillary network, was demonstrated in infants with transposition with and without interventricular septum defect (III, IV)

The pattern of a pulmobronchial artery substituting for a bronchopulmonary artery as described above, was recognized in a few specimens from infants with isolated transposition (III)

Supplementary systemic-artery supply of the lung

In three of the aorta-injected specimens from infants with *isolated transposition* the systemic-artery supply of the lung was further increased through the presence of

3) The *end-to-side* anastomosis the bronchial artery empties into the much wider pulmonary artery

Normal A few anastomoses between the bronchial and pulmonary arteries were demonstrated in 16 per cent of the late fetal and neonatal subjects. Most of the anastomoses were of the *side-to-side* type, with the inner diameter of the transverse vessel varying from 75 to 100 µ. Only one intrapulmonary anastomosis of *end-to-end* type (diameter 50 µ) and one anastomosis of *end-to-side* type (diameter 35 µ) were found in this part of the series (I)

In the series of subjects from infancy and early childhood, arterial bronchopulmonary anastomoses were demonstrated in 80 per cent. Their number varied considerably from subject to subject, and they were particularly numerous in the two oldest (aged 3 years and 8 months, and 4 years and 7 months) There was, however no evidence of gradual increase with age. The most common type of anastomosis is *side-to-side*. Occasionally two or three bronchial-artery branches join to form the "afferent systemic part of an H-anastomosis. The inner diameter of the transverse vessel of the side-to-side anastomoses ranges up to 300 µ. The next most common type of anastomosis is *end to-end*. The pleural anastomoses of this type were found at the mediastinal aspect of the lung or at the interlobar fissures. The inner diameter of the arterial arch ranges up to 250 µ. The least common type of anastomosis is *end-to-side*. The inner diameter of these anastomoses ranges from 25 to 250 µ (II)

The wall structure of the transverse vessel of a *side-to-side* anastomosis is generally similar to that of the contributing bronchial artery. Towards the pulmonary artery however many of the transverse vessels change their mural elastic pattern into pulmonary artery type with an increase in elastic fibers and the appearance of an external elastic lamina. In the anastomoses of *end-to-end* type there is a gradual change in the mural pattern of the arterial arch from bronchial-artery type to pulmonary-artery type with an intermediate arteriolar portion in the smaller anastomoses. In anastomoses of *end-to-side type* the contributing bronchial artery keeps its usual mural structure up to shortly before the point of anastomosis where the mural elastic pattern changes to pulmonary-artery type (I, II)

From the age of four weeks, fibrin thrombi were observed in the lumen of many anastomoses of all types. Most of these thrombi appeared to have been formed recently but some were in an early stage of organization. From the age of two months and a half many of the bronchial arteries involved in arterial bronchopulmonary anastomoses have intimal layers of smooth muscle cells narrowing the lumen. The bronchial arteries forming H-anastomoses, the transverse branch in particular are most commonly affected. A few anastomoses of *side-to-side* and *end to-end* types are completely obliterated by intimal smooth muscle cells and connective tissue. These closed anastomoses were observed from the age of seven months (II)

Transposition of the great arteries Arterial bronchopulmonary anastomoses of *side-to-side* and *end-to-end* types were demonstrated in 50 per cent of the infants with *isolated transposition* The most common type is *end-to-end* The diameter of the anastomoses ranges from 50 to 125 µ (III)

A few anastomoses of all types were demonstrated in two of the seven infants with

multiple small mediastinal arteries, originating from branches of the thoracic aorta. In the injected specimens, these arteries were visible to the naked eye and appeared to enter the pulmonary parenchyma in the same way as the bronchopulmonary arteries (III)

Comment

The existence of focal bronchial artery supply of alveolar walls in the human neonatal lung has been recognized previously by Küttner (26) Konaschko (25) and Cudkowicz & Armstrong (13) These old observations were recently confirmed by Wagenvoort & Wagenvoort (55 56) who also suggested the term 'bronchopulmonary arteries' as mentioned above.

The bronchial arteries are, embryologically derived from the systemic arteries supplying the *plexus pulmonalis communis*. The systemic artery supply of this plexus is established earlier than its connection with the pulmonary arteries (9 10 32, 36, 41 50 57) This double arterial supply of the capillary plexus of the developing lung is still reflected in the late fetal and neonatal lung through the presence of bronchopulmonary arteries. These arteries normally become obliterated during the first few years of postnatal life (II)

The frequent and extensive occurrence of bronchopulmonary arteries and supplementary systemic arteries in transposition of the great arteries — of isolated type in particular — can be interpreted as a retention of the early fetal vascular pattern or as an intrauterine adaptation to the cardiovascular malformation. It becomes more prominent with postnatal age but does not reach the same extent in the presence of an associated interventricular septum defect (III IV)

In transposition of the great arteries, the bronchopulmonary arteries carry poorly oxygenated blood from the transposed aorta to the respiratory surface of the alveoli. The benefit of this would be increased considerably in the presence of increased systemic venous drainage of the lungs, as pointed out by Ferencz (19) The structure of the pulmonary venous system in transposition of the great arteries, however has not been analyzed hitherto

Arterial bronchopulmonary anastomoses

The term arterial anastomosis is used to imply a precapillary communication between two arterial systems Three forms of arterial bronchopulmonary anastomoses have been recognized

1) The *side to-side* (H) anastomosis the more or less parallell branches of the bronchial and pulmonary arteries are connected by a transverse (or oblique) vessel in the form of a one-step ladder
2) The *end to-end* anastomosis an arterial or arteriolar arch is present between a lobular branch of the pulmonary artery leaving (penetrating) the lobulus and a peribronchial or pleural branch of the bronchial artery Since the contributing bronchial artery often shows branches running peripherally to the arterial arch many of these anastomoses are more or less T shaped the stem of the "T" representing the contributing pulmonary artery

3) The *end-to-side* anastomosis the bronchial artery empties into the much wider pulmonary artery

Normal A few anastomoses between the bronchial and pulmonary arteries were demonstrated in 16 per cent of the late fetal and neonatal subjects. Most of the anastomoses were of the *side-to-side* type, with the inner diameter of the transverse vessel varying from 75 to 100 μ. Only one intrapulmonary anastomosis of *end-to-end* type (diameter 50 μ) and one anastomosis of *end-to-side* type (diameter 35 μ) were found in this part of the series (I)

I the series of subjects from infancy and early childhood, arterial bronchopulmonary anastomoses were demonstrated in 80 per cent. Their number varied considerably from subject to subject, and they were particularly numerous in the two oldest (aged 3 years and 8 months, and 4 years and 7 months) There was, however no evidence of a gradual increase with age The most common type of anastomosis is *side-to-sid* Occasionally two or three bronchial artery branches join to form the afferent systemic part of an H-anastomosis. The inner diameter of the transverse vessel of the side-to-side anastomoses ranges up to 300 μ. The next most common type of anastomosis is *end-to-end* The pleural anastomoses of this type were found at the mediastinal aspect of the lung or at the interlobar fissures. The inner diameter of the arterial arch ranges up to 250 μ. The least common type of anastomosis is *end to-side* The inner diameter of these anastomoses ranges from 25 to 250 μ (II)

The wall structure of the transverse vessel of a *side-to-side* anastomosis is generally similar to that of the contributing bronchial artery Towards the pulmonary artery however many of the transverse vessels change their mural elastic pattern into pulmonary artery type with an increase in elastic fibers and the appearance of an external elastic lamina. In the anastomoses of *end-to-end* type there is a gradual change in the mural pattern of the arterial arch from bronchial artery type to pulmonary artery type with an intermediate arteriolar portion in the smaller anastomoses. In anastomoses of *end-to-side type* the contributing bronchial artery keeps its usual mural structure up to shortly before the point of anastomosis where the mural elastic pattern changes to pulmonary artery type (I II)

From the age of four weeks, fibrin thrombi were observed in the lumen of many anastomoses of all types. Most of these thrombi appeared to have been formed recently but some were in an early stage of organization. From the age of two months and a half many of the bronchial arteries involved in arterial bronchopulmonary anastomoses have intimal layers of smooth muscle cells narrowing the lumen. The bronchial arteries forming H-anastomoses, the transverse branch in particular are most commonly affected. A few anastomoses of *sid-to-side* and *end-to-end* types are completely obliterated by intimal smooth muscle cells and connective tissue. These closed anastomoses were observed from the age of seven months (II)

Transposition of the great arteries Arterial bronchopulmonary anastomoses of *side to-side* and *end-to-end* types were demonstrated in 30 per cent of the infants with *isolated transposition* The most common type is *end-to-end* The diameter of the anastomoses ranges from 50 to 125 μ (III)

A few anastomoses of all types were demonstrated in two of the seven infants with

transposition associated with interventricular septum defect The diameter of these anastomoses ranges from 50 to 350 μ (IV)

In one *end to-end* anastomosis, present in a subject with isolated transposition and Type I pattern, there was some stenosis of the lumen on the pulmonary artery side through cellular intimal cushions Otherwise none of the anastomoses demonstrated in the two series of infants with transposition displayed obliterative features and they did not have the mural structure of "Sperr arteries (III IV)

Comment

The *normal* incidence of arterial bronchopulmonary anastomoses is greater *in infancy and early childhood* than in the *late fetal and neonatal period* indicating that anastomoses are formed during the postnatal development of the lung The reversal of the relative frequencies of arterial bronchopulmonary anastomoses and pulmobronchial arteries after the age of two months suggests that anastomoses — of H type at least — result from the establishment of precapillary communications between pulmobronchial arteries and neighboring ordinary *bronchial* arteries (II)

Another difference between the late fetal neonatal period and infancy-early childhood is the postnatal development of *pleural arterial bronchopulmonary anastomoses*. These structures were not demonstrated in the present study of the late fetal and neonatal lung (I) The existence of pleural anastomoses in the human neonatal lung has been claimed however by other investigators (25 26, 53 59)

The theory suggested by Weibel (57) that arterial bronchopulmonary anastomoses present in the fetal lung disappear later in life was recently supported by Wagenvoort & Wagenvoort (56) who demonstrated fibrous obliteration of anastomoses in one infant, aged one year The present study gives further support to this view It is obvious that anastomoses can be obliterated by intimal muscle bundles, fibrin thrombi and connective tissue (II)

It seems probable that obliteration affects anastomoses without shunt function i.e. superfluous vascular channels The development of "Sperr artery structure in arterial bronchopulmonary anastomoses would then be a process of involution rather than a differentiation towards the specialized function of flow regulation attributed to these vessels (24) The variation in the thickness of the intimal smooth muscle bundles in bronchial artery branches involved in anastomoses of side-to-side type is possibly related to an established direction of flow in the anastomosis, as indicated in Table 2.

Table 2

Possible relation between "Sperr"-artery structure and established direction of flow in arterial bronchopulmonary anastomoses of side-to-side (H) type as judged from serial sections

Sperr artery structure particularly prominent in	Presumed direction of flow in anastomosis
afferent BA	PA → BA
efferent BA	PA ← BA
transverse vessel	none
neither	not established

PA = pulmonary artery
BA = bronchial artery

In *transposition of the great arteries* with or without an interventricular septum defect (III IV) the arterial bronchopulmonary anastomoses are essentially normal in type. The over representation of anastomoses of

end-to-end type in specimens from infants with isolated transposition is probably related to the extensive occurrence of bronchopulmonary arteries in these subjects. In regions of the pulmonary parenchyma supplied by bronchopulmonary arteries, there are — as a rule — capillary communications between these arteries and adjacent branches of the pulmonary artery. There is a gradual transition between this pattern and the pattern of small arterial bronchopulmonary anastomoses of end-to-end type (III).

The sources of error (overlapping etc., see p. 70) involved in the demonstration and measuring of pulmobronchial arteries naturally have the same influence on the study of arterial bronchopulmonary anastomoses. As for the pulmobronchial arteries, there is a degree of uncertainty in the classification, counting and measurement of the anastomoses. The figures given above on the incidence and size of anastomoses should therefore be regarded as approximate. The findings of the present study concerning the size of the arterial bronchopulmonary anastomoses in the normal human perinatal lung agree, however, fairly well with recent histologic observations by Wagenvoort & Wagenvoort (55, 56).

The functional significance of the arterial bronchopulmonary anastomoses is probably low both in the normal infant lung and in transposition of the great arteries. Their normal functional capacity is, however, probably somewhat greater in infancy and early childhood than in the late fetal and neonatal period (I, II). In transposition of the great arteries — of isolated type in particular — a more important pathway for the systemic blood to the alveolar capillary bed is offered by the bronchopulmonary arteries (III, IV).

transposition associated with interventricular septum defect The diameter of these anastomoses ranges from 50 to 350 μ (IV)

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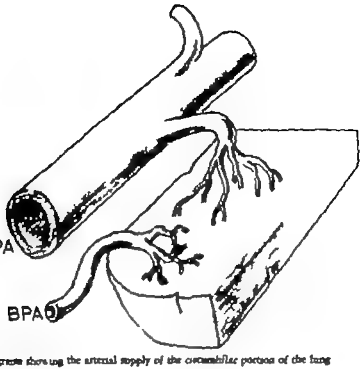
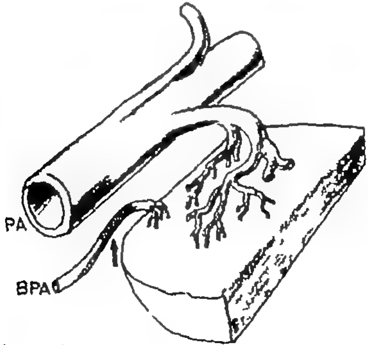


Fig 2 Diagrams showing the arterial supply of the circumlobular portion of the lung

A Normal late fetal and neonatal period The circumlobular portion of the lung is supplied by abrupt branches of the pulmonary artery (PA) and by bronchopulmonary arteries (BPA)



B Normal infancy and childhood Involution with obliteration of bronchopulmonary arteries (BPA, arrow)

CONCLUSION

Normal intrapulmonary arterial pattern The pulmonary arterial system generally branches with the bronchi, with the exception of "abrupt" branches present particularly in the "medullary" zone of the lung

Pulmobronchial arteries occur inconsistently and contribute to the arterial supply of a few bronchi

The ordinary bronchial arteries generally follow the course of the bronchi The diameter of the main bronchial arteries in the hilus of the lung increases with fetal age but is fairly constant during infancy and early childhood From the age of 10 weeks, some of the bronchial arteries have the structure of "Sperr" arteries with intimal bundles of smooth muscle cells Focal bronchial artery supply of small areas of the pulmonary parenchyma proper *via* bronchopulmonary arteries is a regular feature of the late fetal and neonatal lung (Fig 2 A) The bronchopulmonary arteries become narrowed and obliterated in early infancy and can rarely be demonstrated microangiographically after the immediate neonatal period (Fig 2 B)

Arterial bronchopulmonary anastomoses (of side to-side, end to-end and end-to-side types) occur inconsistently They are more numerous in infancy and early childhood than in the late fetal neonatal period The "Sperr"-artery structure of bronchial arteries particularly affects branches involved in arterial bronchopulmonary anastomoses and from the age of seven months some anastomoses are completely obliterated.

The intrapulmonary arterial pattern in transposition of the great arteries Abnormal patterns of the pulmonary arterial system are consistently present, either in the form of funnel shaped narrowing of intralobular arteries (Type I) or in the form of increased tortuosity of intralobular arteries (Type II) Furthermore, in some cases the abrupt branches are abnormal in type with octopus like ramifications.

Pulmobronchial arteries are generally about as frequent as in the normal infant. In many instances, however they diverge from the normal pattern by deviating from the bronchial wall in their terminal course to end as alveolar capillaries

The bronchial arteries are wider than in the normal neonatal lung and supply a large portion of the pulmonary parenchyma proper in the "medullary" zone of the lung *via* bronchopulmonary arteries (Fig 2 C) Obliteration of branches of the pulmonary artery was occasionally observed in areas supplied by bronchopulmonary arteries indicating that the arterial supply of these areas has been taken over by the bronchial arterial system (Fig 2 D)

In some cases the systemic artery supply of the pulmonary parenchyma proper is further increased by small mediastinal arteries running to the neighboring dorsal portion of the lungs

Arterial bronchopulmonary anastomoses occur inconsistently They are few in number and they are usually end to-end

The intrapulmonary arterial pattern in transposition of the great arteries associated with interventricular septum defect The pulmonary arterial pattern is either normal

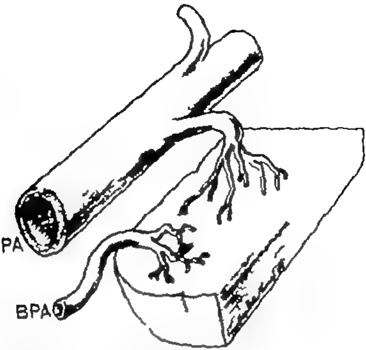
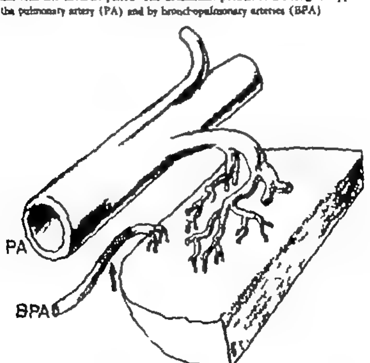


Fig. 2. Diagrams showing the arterial supply of the circumhilar portion of the lung.

A. Normal late fetal and neonatal period. The circumhilar portion of the lung is supplied by abrupt branches of the pulmonary artery (PA) and by bronchopulmonary arteries (BPA).



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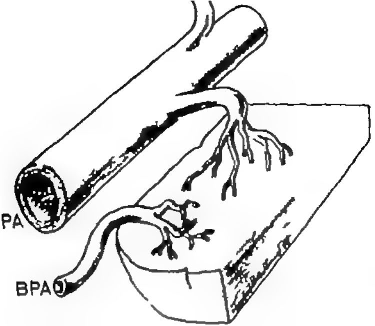

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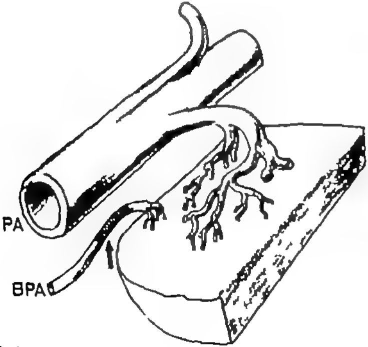

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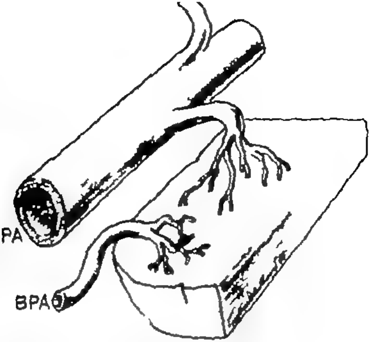

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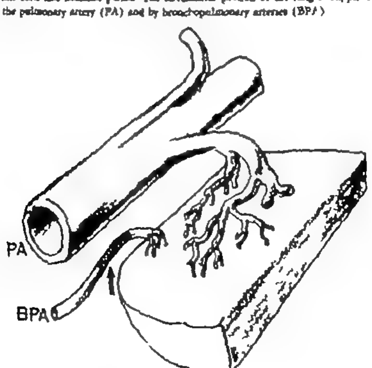

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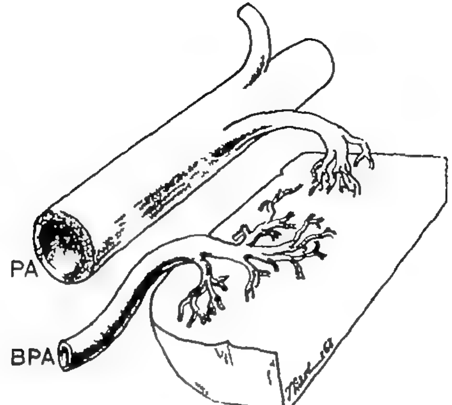
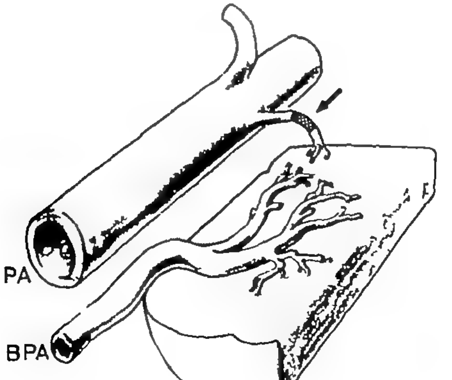


C. Isolated transposition of the great arteries, immediate neonatal period. Wide bronchopulmonary arteries (BPA) enter the circumhilar portion of the lung.



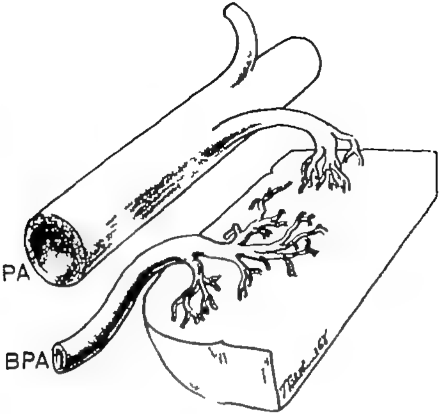
D. Isolated transposition of the great arteries, infancy. The bronchopulmonary arteries (BPA) are further increased in size and some abrupt branches of the pulmonary artery (PA) are obliterated (arrow).

in type or the intralobular arteries are tortuous.

Pulmobronchial arteries are few in number and occur inconsistently. They are generally normal in type and of normal size.

The bronchial artery supply of the pulmonary parenchyma proper via bronchopulmonary arteries, is within normal limits or moderately increased.

Arterial bronchopulmonary anastomoses are inconsistent and few in number. Their structure and size are essentially normal.



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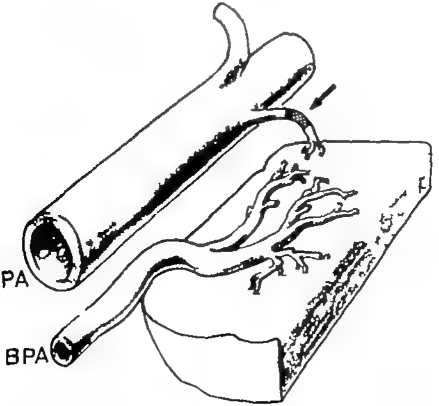

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SUMMARY

Microangiographic and histologic studies of the pulmonary and bronchial arterial systems were carried out on 52 normal human fetuses, infants and children and on a series of 17 infants with transposition of the great arteries isolated or associated with an interventricular septum defect. *Particular attention was paid to various types* of aberrations from the basic arterial pattern arterial bronchopulmonary anastomoses, pulmobronchial arteries and bronchopulmonary arteries.

The arterial bronchopulmonary anastomoses are of essentially the same type in normal cases as in transposition of the great arteries. The normal number of anastomoses is greater in infancy and early childhood than in the late fetal and neonatal period. From the age of a few months, however many of the anastomoses become narrowed or obliterated. Abnormal pattern of the pulmonary arterial system, including abnormal pulmobronchial arteries, is a prominent feature in isolated transposition, less *so in transposition associated with inter*ventricular septum defect. In isolated transposition there is a considerable increase in the bronchial artery supply of the pulmonary parenchyma proper *via* bronchopulmonary arteries. In transposition associated with interventricular septum defect, the bronchial artery supply of the pulmonary parenchyma has a normal extent or is only moderately increased.

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AND HOWARD SPRECHER, PH.D

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INTRODUCTION

The transport and metabolism of lipids by the human placenta is of unknown clinical significance. If we presume that the fetus, like the adult, cannot synthesize the essential fatty acids of the linoleate family then these fatty acids must be derived from the maternal circulation and most likely cross the placenta. The normal growth of newborn infants is dependent upon an adequate supply of the essential fatty acids (1) and fetal growth must be similarly dependent. This is the basis of our interest in placental lipid transport and metabolism.

Previously the placenta has been considered impermeable to most lipids. This has been substantiated by the general lack of correlation between maternal and umbilical cord blood lipid levels (2, 3 4 5 6, 7 8 9). The variables which may obscure such correlation are, of course, the placental and fetal uptake, synthesis, and interconversion of lipids.

The dissimilarity of the fatty acid composition of maternal and umbilical cord blood lipids (2, 4 10, 11 1., 13 14 15) is similarly used as an argument against transport and has the same weakness. Another error in logic in the use of fatty acid compositional studies is that they are frequently calculated as percentages so that no absolute quantity of an individual fatty acid is expressed

Early perfusion and feeding studies in animal showed no or little transport across the placenta of phospholipids (16, 17), cholesterol (18), and fatty acids (19). Recent animal studies, using more physiologic techniques, are showing very significant levels of transport. As always there is the basic problem of extrapolating data from animal experiments to humans.

It is our impression that the maternal circulation is the probable source of a good portion of the placental and fetal lipids and that placental metabolism notably alters maternal lipids before they enter the fetal circulation. The purpose of this review is to discuss those data that support or refute this view

CHANGES IN LIPIDS WITH PREGNANCY AND DELIVERY

During human pregnancy the concentration of every general lipid fraction increases (21 22, 23 .4 25 26, 27 28, 29 30 31 32, 33 34). The only exception to this is the phospholipid, lysolecithin, which decreases (35) The maternal values at delivery are given in Table 1 No cause for the hyperlipidemia of pregnancy is agreed upon. It is interesting to consider the possibility that the placenta and fetus contribute lipids to the maternal circulation causing the hyperlipidemia. Although the hyperlipidemia in the mother decreases in the first post partum days (24 36 37 38) and, in the case of free fatty acids, within sixty minutes (39), normal levels are not reached until two to five days for the free fatty acids (24 37) and two to six months for the other lipid fractions (31 32, 40) This slow decline argues against the simple mechanism of a fetoplacental contribution to the maternal circulation.

One very interesting and unexplained point has arisen from the fatty acid compositional studies. In comparing maternal and fetal fatty acids from cholesterol esters (2, 14) lecithin (2, 4, 15) and cephalin (2, 15) the relative per cent of linoleic acid in the fetus is lower and that of arachidonate higher (see Tables 5 through 7). Does this mean that the maternal arachidonate esters are preferentially crossing the placenta? If so we might expect to see a difference in pregnant and nonpregnant fatty acid patterns in the cholesterol ester lecithin, and cephalin fractions. Very few such studies are either reported and none give enough data for answering this question.

INFANT LIPID CHANGES FOLLOWING DELIVERY

The umbilical cord blood levels of the lipid fractions are presented in Table 1 and are consistently lower than the maternal values (2, 3 4 5 7 13 14 42, 43 44 45 46, 47 48) with the exception of lysolecithin (4 35). Following delivery in-

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Table 2 *Free fatty acid composition*

Patterns from the data of Robertson *et al.* (57). Figures represent the mean area per cent followed by one standard deviation. Figures in parentheses represent the number of samples.

Component	Maternal serum (4)	Perfused placenta (6)	Umbilical cord serum (5)
12:0	0.7 + 0.7	1.0 0.5	1.3 0.6
14:0	5.1 + 2.9	2.0 1.1	6.9 + 3.3
16:0	28.4 5.7	28.8 2.4	37.6 2.8
16:1ω7	3.7 0.6	1.7 + 0.4	3.4 + 1.2
18:0	1.3 2.6	20.6 2.1	15.8 + 7.3
18:1ω9	38.6 7.1	13.4 0.6	23.2 + 5.8
18:2ω6	8.0 2.6	7.7 1.6	7.8 1.7
18:3ω3	0.8 0.9	0.3 0.4	0.2 0.3
20:3ω6	0.8 1.0	3.0 0.9	0.7 + 0.8
20:4ω6	1.5 1.1	21.4 3.1	2.9 1.6

Table 3 *Free fatty acid and adipose fatty acid composition*

Maternal, umbilical, and infant free fatty acids are from the data of Chen *et al.* (10) while the newborn adipose total lipid fatty acid pattern is from the data of Hirsch *et al.* (58). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.

See also footnote, p. 5

Component	Free fatty acids, maternal plasma (8)	Free fatty acids, umbilical vein plasma (11)	Free fatty acids, infant plasma (4 hours old (4)	Total lipid fatty acids, new born adipose (3)
12:0	0.70 + 0.8	1.2 0.8	0.4 + 0.4	N
14:0	2.7 + 1.2	3.5 1.5	2.4 + 0.8	3.0
16:0	29.1 + 3.2	33.7 + 3.4	42.2 2.6	40.2 + 0.9
16:1ω7	8.6 3.6	8.0 3.2	14.4 3.4	14.6 0.3
18:0	9.5 3.1	14.8 3.8	8.6 3.9	5.1
18:1ω9	35.6 + 4.7	28.0 4.9	28.7 + 2.4	25.2 + 1.3
18:2ω6	13.7 + 2.7	10.6 2.6	3.4 1.1	1.3 + 0.1

than at term. This finding is not supported by all the available data (61) and needs to be repeated with larger number of samples.

The presence of linoleic acid and its decline after birth strongly suggest a maternal source. There are no published reports of free fatty acids crossing the placenta in humans. In laboratory animals such as the rabbit C¹ free fatty acids administered to the mother lead to C in the fetal free fatty acids (62). The same is true for the sheep (63). In monkeys free fatty acids are rapidly transferred from mother to fetus. An interesting and contradictory point of this work is that at term the uptake by the placenta and transfer to the fetus of linoleic acid is greater than earlier in gestation (64).

We can only infer that, in humans, as in other animals, free fatty acids may enter the placenta from the maternal circulation and be extruded into the fetal circulation as free fatty acids. But this transfer is apparently not entirely direct or quantitative. It does not, for example, easily explain the high percentage of arachidonic acid found in the free fatty acid fraction of the placenta (see Table). The free fatty acid composition of the placenta is sufficiently different from that of the mother to suggest that some of the components of this free fatty acid pool are derived from other sources than the maternal circulation (57). If transplacental transport of essential fatty acids is primarily as free fatty acids, a very selective mechanism must be at work favoring arachidonic acid. It seems probable that the placenta may alter the pattern of free fatty acids presented to it before they enter the fetal circulation.

The placenta has several interesting possibilities in the realm of free fatty acid metabolism. There is no information to show if placental tissue carries out beta oxidation of fatty acids. The synthesis of long chain fatty acids from C¹ acetate by a purified placental extract is reported. This synthesis is enhanced by estradiol through stimulation of a pyridine nucleotide transhydrogenase. The fatty acid formed is identified as palmitate but no data is given to show if further chain elongation or desaturation occurs (65). If the placenta is capable of converting linoleic acid to arachidonic acid, it could explain the accentuation of arachidonic acid in the placental and fetal lipids.

There is a non-dialyzable material in antepartum maternal serum which liberates free fatty acids from rat adipose tissue. This activity is not

Tables 1 Fatty acid components are expressed in the following manner: the first number represents the number of carbon atoms, following the colon is the number of unsaturated bonds, following the ω the carbon number of the first unsaturated bond counting from the methyl end of the fatty acid. Components preceded by an asterisk are unidentified and expressed by their equivalent chain length. Fatty acids labeled 18:1ω9 and 18:3ω6 may have ω7 fatty acids included in the percentage since these are probably not separated under the reported conditions. The letter N means not reported.

Table 1 *Lipid components at birth*

Values for components 1 through 5 are from the work of Nelson *et al* (3). Total phospholipid value is derived by multiplying the lipid phosphorus in mg per cent by 25 Individual phospholipid values (components 6–11) in maternal and umbilical cord blood are from the data of Zee (4). Individual phospholipid values (components 6–11) in placental tissue are from the data of Nelson *et al* (134). Lipoprotein values (components 12 and 13) are from the data of Brown *et al.* (7).

Component	Mother's blood	Placental tissue	Umbilical cord blood
Microequivalent per L or per K of tissue (wet weight)			
1 Free fatty acids	1250+78	4922+664	586+78
Milligrams per 100 ml or per 100 g of tissue (wet weight)			
2 Free cholesterol	93+7	221+11	29+3
3 Cholesterol ester	224+9	64+8	76+5
4 Triglyceride	159+14	89+7	43+5
5 Phospholipid	316+14	886+39	111+7
Milligrams per 100 ml or per 100 g of tissue (wet weight) of phospholipid phosphorus			
6. Lecithin	6.94+1.27	18.73	2.75+0.47
7 Cephalin	0.75+0.17	N	0.25+0.04
8 Phosphotidyl-ethanolamine	N	11.44	N
9 Phosphatidylserine	N	3.45	N
10. Lysolecithin	0.21+0.09	0.71	0.30+0.07
11 Sphingomyelin	1.59+0.47	5.01	0.84+0.18
Milligrams per 100 ml of lipoprotein lipid			
12. Alpha lipoproteins	257+71	N	147+40
13 Beta lipoproteins	847+176	N	224+61

fant plasma free fatty acid values rise to a maximum between thirty minutes (49) and twelve hours (50) The triglycerides have risen significantly at twelve hours (13) perhaps representing the hepatic incorporation of mobilized free fatty acids into triglycerides. The total cholesterol values do not change in the first twelve hours (13) Certainly there is apparently no acute decline in any lipid fraction upon delivery indicating that either there is at birth no dependence upon maternal or placental lipids or that the infant quickly asserts his control over circulating lipid levels.

Carbohydrate fed newborn infants show no increase in lipoproteins or lipids as long as proteins and amino acids are excluded from their diet (51) This suggests that the elevation in lipids following birth (and perhaps the levels before birth) is a function of the protein level rather than a reflection of placental impermeability to certain lipid classes.

FREE FATTY ACIDS

Transport and metabolism. It is difficult to draw conclusions about the placental transport of free fatty acids at delivery because of the complexity of the free fatty acid changes in the perinatal period in both the mother's and infant's circulation. Maternal circulating free fatty acids rise even more during labour (25 37 52, 53) probably due to endogenous catecholamine release. In the normal infant the rise in the circulating free fatty acid level correlates with a falling glucose level (46 54) and is due to lipolysis as evidenced by an elevation of circulating glycerol (50) These free fatty acids are being oxidized to ketone bodies (55)

When maternal free fatty acid levels are further elevated by epinephrine infusion no change in umbilical cord blood free fatty acids occurs (56) This would argue against transport. However the variables are numerous in such experiments. For example it has been shown that elevating the maternal glucose level leads to an elevated umbilical cord blood glucose level and a lowered umbilical cord blood free fatty acid level This effect occurs with a 5 per cent dextrose solution and no further lowering of the umbilical cord blood free fatty acid level occurs when a 20 per cent dextrose solution is used although the maternal free fatty acid level declines further (40) It may be that phenomena such as this obscure a direct correlation between maternal and fetal free fatty acid levels.

Several studies show that the umbilical cord blood free fatty acid pattern at birth does not resemble the mother's circulating free fatty acid patterns (2, 10, 57) or the newborn's adipose tissue fatty acid pattern (see Tables 2 and 3) (58 59 60) At two to four hours of age the infant's plasma free fatty acids resemble more closely the newborn adipose tissue (10 60) Especially pertinent is the fall in the relative per cent of linoleic acid which we presume to be of maternal origin The reasonable assumption is that, *in utero* the fetal free fatty acids are derived both from fetal sources and selective placental transport from the mother

The triglyceride fatty acid pattern of premature infant adipose tissue more closely resembles that of the mother (58 59) This suggests that earlier in gestation the maternal free fatty acids may contribute more directly to the fetal adipose tissue

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Patterns from the data of Robertson *et al.* (57). Figures represent the mean area per cent followed by one standard deviation. Figures in parentheses represent the number of samples.

Component	Maternal serum (6)	Perfused placenta (6)	Umbilical cord serum (5)
12:0	0.7 0.7	1.0+0.5	1.3 0.6
14 0	3.1 2.9	2.0 1.1	6.9+3.3
16.0	28.4 5.7	28.8+2.4	37.6+2.8
16 1 7	3.7 0.6	1.7+0.4	3.4 1.2
18 0	12.3 2.6	20.6+2.1	15.8+7.3
18 1ω9	38.6 7.1	13.4 0.6	23.2+5.4
18 2ω6	8.0 2.6	7.7 1.6	7.8 3.7
18 3ω3	0.8 0.9	0.5 0.4	0.2 0.5
20 3ω6	[illegible] 1.0	3.0 0.9	0.7+0.8
20 4 6	1.5 1.1	21.4 3.1	3.9 1.6

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Maternal, umbilical, and infant free fatty acids are from the data of Chen *et al.* (10) while the newborn adipose total lipid fatty acid pattern is from the data of Hirsch *et al.* (38). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.

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14 0	2.7 +1.2	3.5+1.5	2.4+0.8	3.0
16 0	29.1 3.2	31.7+3.4	42.2+ [illegible]	40.2+0.9
16. 1ω7	8.6 +3.6	8.0+3.2	14.4+3.4	14.6+0.3
18 0	9.5 2.1	14.0+3.8	8.6 3.9	5.1
18 1 9	35.6 +4.7	28.0+4.9	28.7 2.4	25.2+1.3
18·2ω6	13.7 +2.7	10.6+2.6	3.4+1.1	1.3+0.1

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Several studies show that the umbilical cord blood free fatty acid pattern at birth does not resemble the mother's circulating free fatty acid patterns (2, 10, 57) or the newborn's adipose tissue fatty acid pattern (see Tables 2 and 3) (58, 59, 60). At two to four hours of age the infant plasma free fatty acids resemble more closely the newborn adipose tissue (10, 60). Especially pertinent is the fall in the relative per cent of linoleic acid which we presume to be of maternal origin. The reasonable assumption is that, *in utero* the fetal free fatty acids are derived both from fetal sources and selective placental transport from the mother.

The triglyceride fatty acid pattern of premature infant adipose tissue more closely resembles that of the mother (58, 59). This suggests that earlier in gestation the maternal free fatty acids may contribute more directly to the fetal adipose tissue

Table 4 *Fatty acid composition of triglycerides*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while placental tissue data are from Sprecher and Robertson (81). *Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.*

See also footnote, p. 5

Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (7)	Amnion (7)	Umbilical cord serum (16)
14 0	2.3+0.7	1.5+0.7	2.9+0.6	2.9+1.0	2.3+0.7
16 0	39.4+3.4	29.6+3.1	31.3+4.5	40.6+2.8	34.2+3.5
16 1ω7	3.4+1.1	3.1+0.8	4.6+1.5	5.8+1.1	5.6+1.3
18 0	2.1+0.4	9.2+1.3	11.2+3.7	7.3+1.4	3.9+1.0
18 1ω9	43.9 3.1	21.4+2.9	22.0+2.8	19.4+2.9	38.6+5.4
18 2ω6	7.2+2.3	11.2+1.4	8.5+2.6	7.9+1.3	9.1+2.3
18 3ω3	[illegible]				Trace
20 3ω6		5.2+2.1	3.6+3.2	3.3+0.8	Trace
20 4ω6	0.8+0.5	11.0 2.5	6.5+2.4	5.7+1.4	2.8
22 4ω6	N	1.9 0.5	2.2+0.9	1.5+0.4	[illegible]
[illegible] 5ω6	N	1.4 0.6	1.0+0.7	0.7+0.2	N
22 6ω3	N	2.5+1.0	2.0+1.9	1.6+0.4	2.5+1.1
24 4ω6	N	0.5 0.3	1.4 0.7	0.9+0.6	N
Unident	N	1.6	2.9	2.6	N

fatty acids of the maternal triglycerides do not appear in the fetal triglycerides (71). The fatty acid pattern of triglycerides in human tissue is presented in Table 4.

It is hard to know the significance of much enzymatic data. For example it is reported that the clearing factor of post-heparin maternal plasma is progressively depressed during the second and third trimesters and begins returning to normal one to four days after delivery (72). Does this indicate that there is less lipoprotein lipase at the placental surface during late pregnancy and therefore less formation of diglycerides and monoglycerides to enter the placenta? Lipoprotein lipase activity is present in placental tissue (73) and in newborn plasma before feeding (74).

Lipase activity is present in placental tissue as measured by the hydrolysis of triacetin (75). Amnion cell homogenates hydrolyze triolein (76). The histochemical search for lipases in placental tissue varies from negative results (77) to the finding of lipase activity in very early syncytial cells and its persistence until term with a sharp decline at parturition (78). Serum lipase activity is present in umbilical cord blood indicating its presence in fetal tissues at birth (79). Placental lipase activity should be studied using those triglycerides present in maternal and placental tissue.

Placental tissue will incorporate C^{14} acetate into triglycerides. Because of differences in the rate at which free fatty acids, monoglycerides, diglycerides, and triglycerides are labeled, it is suggested that there is a slow synthetic pathway in which palmitic and stearic acid are synthesized *de novo* and then esterified to form monoglyceride, diglyceride, and triglyceride, and a rapid pathway where a labeled polyenoic acid is esterified to diglyceride to form triglyceride. It is also suggested, without proof, that this polyenoic acid is arachidonic acid formed from the chain desaturation and elongation of linoleate (80). This reaction has not yet been demonstrated directly in placental tissue. The proposed mechanism of rapid triglyceride synthesis utilizing arachidonic acid would explain the high relative percent of arachidonic acid (see Table 4) in placental tissue triglycerides (81).

Summary (see Fig. 2). It seems probable that triglycerides do not pass intact across the placenta. However maternal triglycerides at the placental border may be acted upon by lipoprotein lipase to produce fatty acids and other glycerides which may enter the placental cells. Placental tissue synthesizes triglycerides and these are probably subject to lipase activity and contribute their fatty acids to the placental fatty acid pool which may then be passed into the fetal circulation. The triglycerides of the fetal circulation probably arise from the liver synthesis of triglycerides although triglycerides synthesized in the placenta may be

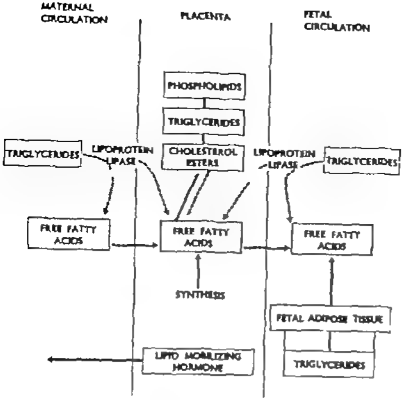

Fig. 1

present in postpartum serum. It is found in placental homogenates and in the serum of a non-pregnant patient with choriocarcinoma (66) Therefore it originates in the placenta. It is probably similar to the previously described growth hormone-prolactin produced by the placenta and known to have free fatty acid mobilizing capabilities (67) It is suggested that this lipid mobilizing action leads to glucose conservation in the mother and thereby assures maximum transfer of glucose to the fetus The levels of this hormone in the fetal circulation are quite low and probably exert no effect on fetal lipid metabolism (68) It would be interesting to know if the free fatty acids mobilized by this substance are the same as those mobilized by hypoglycemia in a non-pregnant subject.

Summary (see Fig 1) It appears likely that specific free fatty acids in the maternal circulation may enter the placental tissue and pass into the fetal circulation. The free fatty acid pattern of the infant's circulation after birth (and perhaps before birth) may be altered by the mobilization of free fatty acids from fetal adipose tissue. Whether the free fatty acid pattern in the fetal circulation is altered by the presence of fatty acids synthesized or altered by the placenta or in other areas of the fetus is not known The free fatty acid pool of the placenta may be added to by the hydrolysis of maternal triglycerides at the placental membrane by lipoprotein lipase. Hydrolysis of glycerides, cholesterol esters, and phospholipids within the placenta may also add to the placental and fetal free fatty acid pool The placenta, itself releases a lipid mobilizing hormone which causes an increased mobilization of free fatty acids in the mother

TRIGLYCERIDES

Transport and metabolism. There are no reported studies dealing directly with the passage of intact triglycerides across the placenta. Many animal studies using diets of different oils whose triglycerides contain various fatty acid patterns have been reported. The only available work in humans involves mothers given cod liver oil or sesame oil prior to surgical abortions. This meagre data suggests that the triglyceride fatty acids may cross the placenta (69) In animals such as the guinea pig the data is clearer but not revealing as to the form or mechanism of passage (70) Data from the fatty acid patterns of lipids in fetal and maternal sheep shows that the exogenous trans-

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16:0	39.4±3.4	29.6±3.1	31.3±4.5	40.6±2.8	34.2±3.5
16:1ω7	3.4±1.2	3.1±0.8	4.6±1.5	5.8±1.1	5.6±1.3
18:0	2.1±0.4	9.2±1.3	11.2±3.7	7.3±1.4	3.9±1.0
18:1ω9	43.9±3.1	21.4±2.9	22.0±2.8	19.4±2.9	38.6±5.4
18:2ω6	7.2±2.3	11.2±1.4	8.5±2.6	7.9±1.3	9.1±2.3
18:3ω3	1.0				Trace
20:3ω6		5.2±2.1	3.6±3.2	3.3±0.8	Trace
20:4ω6	0.8±0.5	11.0±2.5	6.5±2.4	3.7±1.4	2.8
22:4ω6	N	1.9±0.5	2.2±0.9	1.5±0.4	N
22:5ω6	N	1.4±0.6	1.0±0.7	0.7±0.2	N
22:6ω3	N	2.5±1.0	2.0±1.9	1.6±0.4	2.5±1.1
24:4ω6	N	0.5±0.3	1.4±0.7	0.9±0.6	N
Unident.	N	1.6	2.9	2.6	N

fatty acids of the maternal triglycerides do not appear in the fetal triglycerides (71). The fatty acid pattern of triglycerides in human tissue is presented in Table 4.

It is hard to know the significance of much enzymatic data. For example it is reported that the clearing factor of post-heparin maternal plasma is progressively depressed during the second and third trimesters and begins returning to normal one to four days after delivery (72). Does this indicate that there is less lipoprotein lipase at the placental surface during late pregnancy and therefore less formation of diglycerides and monoglycerides to enter the placenta? Lipoprotein lipase activity is present in placental tissue (73) and in newborn plasma before feeding (74).

Lipase activity is present in placental tissue as measured by the hydrolysis of triacetin (75). Amnion cell homogenates hydrolyze triolein (76). The histochemical search for lipases in placental tissue varies from negative results (77) to the finding of lipase activity in very early syncytial cells and its persistence until term with a sharp decline at parturition (78). Serum lipase activity is present in umbilical cord blood indicating its presence in fetal tissues at birth (79). Placental lipase activity should be studied using those triglycerides present in maternal and placental tissue.

Placental tissue will incorporate C^{14} acetate into triglycerides. Because of differences in the rate at which free fatty acids, monoglycerides, diglycerides, and triglycerides are labeled, it is suggested that there is a slow synthetic pathway in which palmitic and stearic acid are synthesized *de novo* and then esterified to form monoglyceride, diglyceride, and triglyceride, and a rapid pathway where a labeled polyenoic acid is esterified to diglyceride to form triglyceride. It is also suggested, without proof, that this polyenoic acid is arachidonic acid formed from the chain desaturation and elongation of linoleate (80). This reaction has not yet been demonstrated directly in placental tissue. The proposed mechanism of rapid triglyceride synthesis utilizing arachidonic acid would explain the high relative percent of arachidonic acid (see Table 4) in placental tissue triglycerides (81).

Summary (see Fig. 2). It seems probable that triglycerides do not pass intact across the placenta. However maternal triglycerides at the placental border may be acted upon by lipoprotein lipase to produce fatty acids and other glycerides which may enter the placental cells. Placental tissue synthesizes triglycerides and these are probably subject to lipase activity and contribute their fatty acids to the placental fatty acid pool which may then be passed into the fetal circulation. The triglycerides of the fetal circulation probably arise from the liver synthesis of triglycerides although triglycerides synthesized in the placenta may be another source.

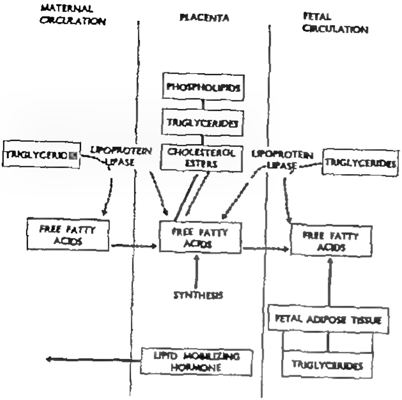

Fig. 1

present in postpartum serum. It is found in placental homogenates and in the serum of a non pregnant patient with choriocarcinoma (66). Therefore it originates in the placenta. It is probably similar to the previously described growth hormone prolactin produced by the placenta and known to have free fatty acid mobilizing capabilities (67). It is suggested that this lipid mobilizing action leads to glucose conservation in the mother and thereby assures maximum transfer of glucose to the fetus. The levels of this hormone in the fetal circulation are quite low and probably exert no effect on fetal lipid metabolism (68). It would be interesting to know if the free fatty acids mobilized by this substance are the same as those mobilized by hypoglycemia in a non-pregnant subject.

Summary (see Fig 1) It appears likely that specific free fatty acids in the maternal circulation may enter the placental tissue and pass into the fetal circulation. The free fatty acid pattern of the infant's circulation after birth (and perhaps before birth) may be altered by the mobilization of free fatty acids from fetal adipose tissue. Whether the free fatty acid pattern in the fetal circulation is altered by the presence of fatty acids synthesized or altered by the placenta or in other areas of the fetus is not known. The free fatty acid pool of the placenta may be added to by the hydrolysis of maternal triglycerides at the placental membrane by lipoprotein lipase. Hydrolysis of glycerides, cholesterol esters, and phospholipids within the placenta may also add to the placental and fetal free fatty acid pool. The placenta, itself releases a lipid mobilizing hormone which causes an increased mobilization of free fatty acids in the mother

TRIGLYCERIDES

Transport and metabolism There are no reported studies dealing directly with the passage of intact triglycerides across the placenta. Many animal studies using diets of different oils whose triglycerides contain various fatty acid patterns have been reported. The only available work in humans involves mothers given cod liver oil or sesame oil prior to surgical abortions. This meagre data suggests that the triglyceride fatty acids may cross the placenta (69) In animals such as the guinea pig the data is clearer but not revealing as to the form or mechanism of passage (70) Data from the fatty acid patterns of lipids in fetal and maternal sheep shows that the exogenous trans-

Table 4. *Fatty acid composition of triglycerides*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while placental tissue data ar from Sprecher and Robertson (81). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses re present the number of samples.

See also footnote, p 5

Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (7)	Amnion (7)	Umbilical cord serum (16)
14 0	2 3+0.7	1.5+0.7	2 9+0 6	2.9+1 0	2.1+0.7
16. 0	39 4+3.4	29.6+3.1	31.3+4 5	40 6+2.8	34.2+3.5
16: 1ω7	3.4+1.1	3.1+0.8	4 6+1.5	5 8+1.1	5.6+1.3
18 0	2.1+0.4	9.2+1.3	11.2+3.7	7.3+1 4	3.9+1.0
18, 1ω9	43 9+3.1	21 4+2 9	22.0+2 8	19 4+2.9	38 6+5 4
18 2ω6	7.2+2.3	11.2+1 4	8.5+2 6	7.5+1.3	9 1+2.3
18 3ω3	1.0				Trace
20 3ω6		5.2+2.1	3.6+1.2	3.3+0.8	Trace
20 4ω6	0.8+0.5	11.0+2.5	6.5+2 4	5 7+1.4	2 8
22: 4ω6	N	1.9+0 5	2.2+0.9	1.5+0 4	N
22 5ω6	N	1.4+0 6	1.0+0.7	0.7+0 2	N
22 6ω3	N	2.5+1.0	2 0+1.9	1 6+0.4	2.5+1 1
24 4ω6	N	0.5 0.3	1 4+0 7	0.9+0 6	N
Undeter	N	1.6	2 9	2.6	N

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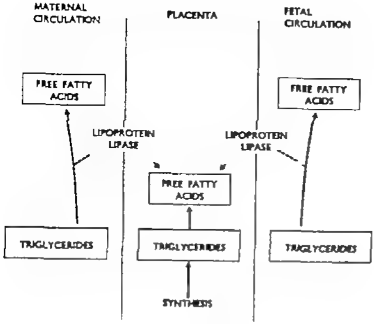


Fig. 2

CHOLESTEROL AND CHOLESTEROL ESTER

Transport and metabolism In the pregnant *rat* fed deuterated cholesterol the cholesterol reaches fetal tissues (82) In the *rat* about 80 percent of the placental cholesterol is derived from the maternal circulation and about 20 percent from cholesterol synthesized in the fetus or placenta. In the *rat* fetus the percent of cholesterol derived from the maternal circulation decreases from about 50 to 70 per cent at twelve to thirteen days of gestation to 15 to 20 per cent at the twentieth day of gestation (83) Similar results are reported with *rabbits* and *guinea pigs* In the *guinea pig* when the mother is fed a cholesterol free diet 20 to 24 per cent of the fetal serum cholesterol is derived from the mother When the mother s diet contained cholesterol 52 to 65 per cent of the fetal serum cholesterol was derived from the mother In both cases the newborn *guinea pig s* circulating level of cholesterol was the same (84) This is a striking example of the fetal control of circulating lipid levels in the presence of varying degrees of placental transport. It also demonstrates the error in presuming no placental transport when maternal and fetal circulating lipid levels show no correlation.

In these studies no data are presented regarding the transfer of cholesterol esters. In the human maternal circulation one source of cholesterol esters is the enzymatic transfer of a fatty acid from lecithin to cholesterol (85) If cholesterol esters do not cross the placenta, the rate of this *transesterification reaction may* determine how much free cholesterol is available for transfer The transesterification reaction occurs also in the newborn infant s blood (86) This is one possible explanation of the higher relative per cent of arachidonic acid in umbilical cord cholesterol esters. When absolute levels of individual cholesterol esters are measured it is found that the ratio of fetal to maternal cholesteryl arachidonate is greater in term than in premature infants (1) The cause of this variation with gestational age is unknown

In placental tissue cholesterol is synthesized *de novo* from acetate and mevalonate. However the synthesis of cholesterol is minimal compared to other sterols (87) Placental tissue will also form cholesterol esters from fatty acids and endogenous cholesterol (76 88) Since the free fatty acid pool of the placenta contains a high relative per cent of arachidonic acid (see Table 2) cholesterol esters formed in the placenta should contain relatively large amounts of arachidonic acid. As can be seen in Table 5 placental tissue falls between maternal and fetal blood in its relative per cent of arachidonic acid These data do not allow any conclusions about the origin of *fetal cholesterol* esters Apparently cholesterol esters are not hydrolyzed by the placenta (76)

Table 5 *Fatty acid composition of cholesterol esters*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) hile placental fatty acids are from Sprecher *et al.* (24). Figures represent the mean area per cent followed by one standard deviation. The figures in parenthese represent the number of samples.
See also footnote, p. 5

Component	Maternal serum (16)	Perfused placenta (5)	Chorion leave (8)	Amnion (5)	Umbilical cord serum (16)
14 0	1.5+0 7	2 4+0.3	3.3+0 8	2 9+0.7	1.2+0.4
15 45	N	1.6+1.2	1 4+0.7	3.3+1.6	N
16 0	14.9 1.2	13.7+1.8	15.1+2.9	19 6+3.0	24.4+1.8
16 1w7	6 2 0 5	3.1+1.9	4 2+0 7	8 0+0 5	8.6+1.9
17 45	N	1.2 0.7	1 6 0.5	2 1+0 3	N
18 0	0 5 0.2	3 6+1 0	8 0+1.4	4.5+1.5	2.0+0 7
18 1w9	29.5 4 0	21 1 0 8	29 9+3.7	21.9+2.5	35 9+3.1
18 2w6	41 8 5.0	33 3+3.1	14 7+2 4	21.4+4 5	15 4+3.5
18 3w3	1 1 0.5	0.9+0.2	2.1 0 9	1.2+0 4	0.4
*21 40	N	0 8+0 6	1 7+0 9	2.1+1 2	N
20 3w6	0 6+0 2	3 0+1 4	3.1+0 9	2.3+1 0	1.1+0.4
20 4 6	3 6 1 1	8.0+1 6	8.7+1 7	6 6+1.3	10 0 2.5
22 4w6	N	1 4+0 3	2.6+1.5	2.3+0.5	N
22 5w6	N	0 9+0 5	1.3+0.3	0 6+0.2	N
22 6w3	N	1 1+0 5	1 6+1 1	0 8 0.2	N

Summary (see Fig. 3). It seems probable that cholesterol crosses from the maternal to the fetal circulation No information about cholesterol esters is available. In placental tissue cholesterol can be synthesized *de novo* and then esterified with fatty acid. It is unknown if the cholesterol esters formed in the placenta will enter the fetal circulation. Cholesterol esters are apparently not hydrolyzed in placental tissue. In the maternal and fetal serum cholesterol esters are formed by the transfer of a fatty acid from lecithin to cholesterol.

PHOSPHOLIPIDS

Transport and metabolism. In the pregnant *rat* injected with labelled phospholipids small amounts of radioactivity are found in the fetal phospholipids (16). In *rabbits* similarly treated the

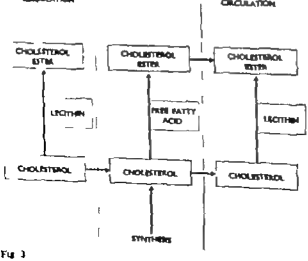
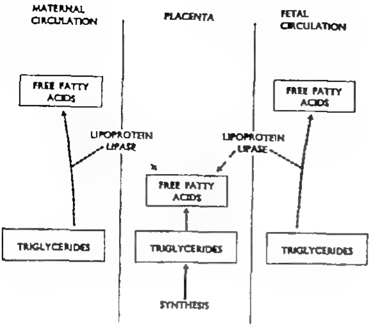


Fig 3



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In placental tissue cholesterol is synthesized *de novo* from acetate and mevalonate. However the synthesis of cholesterol is minimal compared to other sterols (87) Placental tissue will also form cholesterol esters from fatty acids and endogenous cholesterol (76 88) Since the free fatty acid pool of the placenta contains a high relative per cent of arachidonic acid (see Table 2) cholesterol esters formed in the placenta should contain relatively large amounts of arachidonic acid. As can be seen in Table 5 placental tissue falls between maternal and fetal blood in its relative per cent of arachidonic acid. These data do not allow any conclusions about the origin of fetal cholesterol esters. *Apparently cholesterol esters are not hydrolyzed* by the placenta (76)

Table 5 *Fatty acid composition of cholesterol esters*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while placental fatty acids are from Sprecher *et al.* (88) Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.

See also footnote, p. 5

Component	Maternal serum (16)	Perfused placenta (5)	Chorion leave (8)	Amnion (5)	Umbilical cord serum (16)
14 0	1.5+0 7	2.4+0 3	3 3+0 8	2 9 0.7	1.2+0.4
15.45	N	1.6+1.2	1.4+0.7	3.3+1.6	N
16 0	14 9+1 2	15.7+1.8	15.1+2 9	19.6+3 0	24 4+1.8
16 1w7	6 2+0 5	5.1+1.9	4 2+0.7	8 0+0 5	8.6+1.9
17 45	N	1.2+0.7	1.6+0 5	2.1+0 3	N
18 0	0.5+0 2	3.6+1.0	8 0+1 4	4 5+1.5	2.0+0.7
18 1w9	29.5 4 0	21 1+0 8	29 9+1.7	21.9+2 5	35 9+5.1
18 2w6	41.8+5 0	33 3+5 1	14 7+2.4	21 4+4 5	15 4+3.5
18 3w3	1 1+0 5	0 9+0 2	2.1+0.9	1.2+0 4	0 4
*21 40	N	0 8 0 6	1 7+0.9	2.1+1.2	N
20 3w6	0 6 0 2	3 0+1 4	3.1+0 9	2.3+1.0	1 1+0.4
20 4 6	3.6 1 1	8 0+1 6	8.7+1 7	6 6+1.3	10.0+2 5
22. 4w6	N	1 4 0.3	2.6+1.5	2 3+0.5	N
22 5w6	N	0 9+0.5	1.3+0 3	0 6+0 2	N
22 6w3	N	1.1 0 5	1.6+1 1	0 8+0.2	N

Summary (see Fig. 3) It seems probable that cholesterol crosses from the maternal to the fetal circulation. No information about cholesterol esters is available. In placental tissue cholesterol can be synthesized *de novo* and then esterified with a fatty acid. It is unknown if the cholesterol esters formed in the placenta will enter the fetal circulation Cholesterol esters are apparently not hydrolyzed in placental tissue. In the maternal and fetal serum cholesterol esters are formed by the transfer of a fatty acid from lecithin to cholesterol.

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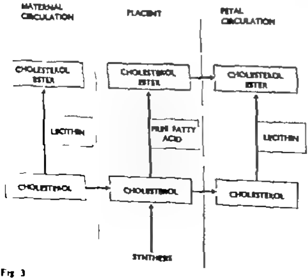

Fig 3

Table 6. *Fatty acid composition of lecithin*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while the placental fatty acids are from Robertson *et al* (88). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.

See also footnote, p. 5

Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (6)	Amnion (5)	Umbilical cord serum (16)
14 0	0.6+0.2	0.4+0.1	2.8+0.8	1.6+0.4	0.5+0.2
15.83	N	1.0+0.2	2.7+0.4	3 1+0.5	N
16 0	42.9+3.3	37.0+3 1	30.4+..7	36.3+3.2	40 1+3.5
16 1w7	0.8	1 4+0.3	3 0+0 8	5 6+1.2	0.7
18 0	8.4+1 1	11.8+0.7	15 9+1.5	11 7+1 1	15 0+1.5
18 1w9	16.5+2.3	10.9+1.0	19 1+1 4	22.1+1.9	12.4+2.3
18 2w6	18 4+2.4	8.1+0.9	7 1+1 9	7.3+1 6	7.0+1.3
20 3w6	3 0+0.6	4.2+0.9	1.5+1.3	2.1+0.2	4 9+0.7
20 4w6	5 7+1 0	21.5+1 8	13 6+1 0	7 7+1.8	13 9+2.1
22. 4w6	N	0.8+0.2	1 7+0.4	0 7+0.6	N
22 5w6	N	0.7	0.5+0 1	0.3+0.1	N
22. 6w3	2.8+0.8	1.5	0.9+0.2	0.8+0.3	5.2+1 4

placenta takes up maternal circulating phospholipids and apparently they are not passed to the fetus (89)

In *sheep* there is a close resemblance in the exogenous fatty acid composition of maternal and fetal phospholipids which suggests the possibility of direct transfer across the placenta (71) The fatty acid patterns in human tissues are presented in Tables 6 and 7 It is noteworthy that, in the fatty acids of the lecithin fraction of perfused placenta and chorion laeve, the fetal pattern of relatively high values of arachidonic acid and low values of linoleic acid is present (see Table 6) This may indicate that the difference in maternal and fetal arachidonic acid metabolism is established at the placenta. It is interesting to speculate that the difference between the mother and fetus in the phospholipid fatty acid pattern represents selective fatty acid transport across the placenta as phospholipid esters In studies describing the

Table 7 *Fatty acid composition of cephalin*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while placental tissue data are from Sprecher and Robertson (15). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.

See [illegible]lso footnote, p 5

Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (6).	Amnion (5)	Umbilical cord serum (16)
14 0	1 2	0.7+0.3	0.5+0.1	0.7+0.3	1 1
15.83	N	10.0+1 3	10.0+0.7	16.6 2.9	N
16 0	22.4+3 4	6.1+0.4	5 0 1.3	5.2+1.2	21.2 5.2
16 1w7	N	0.4+0.2	1 0 0.6	1.3 0.2	N
17.25	N	7 6+1 9	8 8+2.0	12.1 0 9	N
17 75	N	1 7+0.5	2 9+1 1	5.8 1 7	N
18 0	21.0+3 5	11 6 1.3	16 1 1.2	6.8 1 3	18.5 2 9
18 1w9	12.8+2.2	11.0+0 9	10.8 3 7	14 7 4 3	9 9 2.1
18 2w6	11.8+1.8	4 9 0.9	3.5 1.6	2.2 0 6	4 4 1.0
20 3w6		2.6 ..1	1.5 0 7	1.5 0.3	
20 4w6	15.3+2.7	[illegible]7 8+2.1	29.3+3 4	24 7 2.9	23.2 3 0
22 4w6	N	2.8+0.5	4.2+1 7	1 6 0.4	
22. 5w6	N	3 1+0.7	1.5 0 6	0.8 0 3	
22. 5w3	N	1 0 0.2	0.7+0.3	0.4 0 1	
22 6w3	12 5+2.1	8.1+1.3	3.3+1.5	4.5 2.2	15.7 3 7

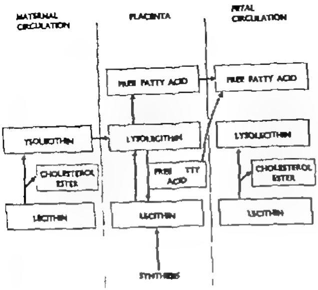

Fig. 4

decrease in maternal lysolecithin during pregnancy it is suggested that the human placenta may remove lysolecithin from the circulation (26). In placental tissue lysolecithin is esterified with a fatty acid to form lecithin (90). This enzyme is known, in other tissues, to preferentially esterify the more unsaturated fatty acids to form lecithin (91). Therefore the specificity of this enzyme may explain the high relative per cent of arachidonic acid in placental tissue. In the *rat* maternal circulating lysolecithin is removed from the circulation by the placenta and esterified to placental lecithin (92). If the lecithin so formed enters the fetal circulation an explanation would be provided for the high relative per cent of fetal lecithin arachidonic acid. However in the pregnant rat infused with P^{32} labelled lysolecithin no radioactivity is found in the fetus (92). Alternatively if the lecithin formed in the placenta were to release its fatty acid at the fetal side of the syncytial cell, the transport of individual fatty acids as phospholipid esters would be complete. If this cycle occurs there should be measurable lecithinase activity in placental cells. Minimal lecithinase activity is reported in the *rat* placenta (93), but none is found in the human placenta (94). Therefore transport of fatty acids to the fetus as phospholipid esters remains doubtful. These investigations should be extended to the ethanolamine and serine phospholipids.

Phospholipids are synthesized in the placenta as evidenced by the incorporation of P^{32} into all phospholipid fractions in incubations utilizing placental tissue slices. This incorporation is reportedly stimulated by the addition of estradiol to the incubation (95). In placental homogenates of twenty week old placentas, as contrasted to term placentas, no phospholipid is synthesized from C^{14} acetate (96). In the *rat* the incorporation of P^{32} into lecithin, lysolecithin, and phosphatidylethanolamine increases markedly as gestation progresses (97). This again suggests a possible dependency on maternal lipids in early pregnancy.

It should be mentioned that several authors studying the transport of amino acids across the rat placenta have described a phosphatido-peptide fraction in the placenta which may be involved in this transport (98, 99). These findings merit further study.

Summary (see Fig. 4). It is probable that intact phospholipids enter the placenta from the maternal circulation but do not pass directly into the fetal circulation. Maternal lysolecithin may well be the precursor of placental lecithin. The fate of lecithin synthesized in the placenta is unknown. The possibility of it acting as a specific fatty acid carrier to the fetal circulation is doubtful since the hydrolysis of lecithin apparently doesn't occur in placental tissue.

Table 6 *Fatty acid composition of lecithin*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while the placental fatty acids are from Robertson *et al.* (88). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.
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Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (6)	Amnion (5)	Umbilical cord serum (16)
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15:83	N	1.0+0.2	2.7+0.4	3.1+0.5	N
16:0	42.9+3.3	37.0+3.1	30.4+2.7	36.3+3.2	40.1+3.5
16:1ω7	0.8	1.4+0.3	3.0+0.8	5.6+1.2	0.7
18:0	8.4+1.1	11.8+0.7	15.9+1.5	11.7+1.1	15.0+1.5
18:1ω9	16.5+2.3	10.9+1.0	19.1+1.4	22.1+1.9	12.4+2.3
18:2ω6	18.4+2.4	8.1+0.9	7.1+1.9	7.3+1.6	7.0+1.3
20:3ω6	3.0+0.6	4.2+0.9	1.5+1.3	2.1+0.2	4.9+0.7
20:4ω6	5.7+1.0	21.5+1.8	13.6+1.0	7.7+1.8	13.9+2.1
22:4ω6	N	0.8+0.2	1.7+0.4	0.7+0.6	N
22:5ω6	N	0.7	0.5+0.1	0.3+0.1	N
22:6ω3	2.8+0.8	1.5	0.9+0.2	0.8+0.3	5.2+1.4

placenta takes up maternal circulating phospholipids and apparently they are not passed to the fetus (89)

In *sheep* there is a close resemblance in the exogenous fatty acid composition of maternal and fetal phospholipids which suggests the possibility of direct transfer across the placenta (71). The fatty acid patterns in human tissues are presented in Tables 6 and 7. It is noteworthy that, in the fatty acids of the lecithin fraction of perfused placenta and chorion laeve, the fetal pattern of relatively high values of arachidonic acid and low values of linoleic acid is present (see Table 6). This may indicate that the difference in maternal and fetal arachidonic acid metabolism is established at the placenta. It is interesting to speculate that the difference between the mother and fetus in the phospholipid fatty acid pattern represents selective fatty acid transport across the placenta as phospholipid esters. In studies describing the

Table 7 *Fatty acid composition of cephalin*

Maternal and umbilical cord fatty acids are from the data of Renkonen (2) while placental tissue data are from Sprecher and Robertson (15). Figures represent the mean area per cent followed by one standard deviation. The figures in parentheses represent the number of samples.
See also footnote p. 5

Component	Maternal serum (16)	Perfused placenta (7)	Chorion laeve (6).	Amnion (5)	Umbilical cord serum (16)
14:0	1.2	0.7+0.3	0.5+0.1	0.7+0.3	1.1
15:83	N	10.0+1.3	10.0+0.7	16.6+2.9	N
16:0	22.4+3.4	6.1+0.4	5.0 1.3	5.2+1.2	21.2 5.2
16:1ω7	N	0.4+0.2	1.0 0.6	1.3 0.2	N
17:25	N	7.6+1.9	8.8 2.0	12.1+0.9	N
17:75	N	1.7+0.5	2.9 1.1	5.8 1.7	N
18:0	21.0+3.5	11.6+1.3	16.1 1.2	6.8+1.3	18.5+2.9
18:1ω9	12.8−2.2	11.0+0.9	10.8+3.7	14.7+4.3	9.9 2.1
18:2ω6	11.8+1.8	4.9 0.9	3.5 1.6	2.2+0.6	4.4 1.0
20:3ω6		2.6+2.1	1.5 0.7	1.5 0.3	
20:4ω6	15.3+2.7	27.8+2.1	29.3+3.4	24.7 2.9	23.2 3.0
22:4ω6	N	2.8+0.5	4.2+1.7	1.6 0.4	
22:5ω6	N	3.1+0.7	1.5+0.6	0.8+0.3	
22:5ω3	N	1.0+0.2	0.7+0.3	0.4 0.1	
22:6ω3	12.5+2.1	8.1+1.3	3.3+1.5	4.5 2.2	15.7 3.7

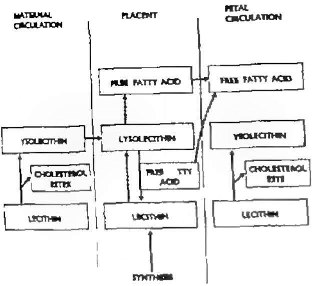

Fig. 4

decrease in maternal lysolecithin during pregnancy it is suggested that the human placenta may remove lysolecithin from the circulation (26) In placental tissue lysolecithin is esterified with a fatty acid to form lecithin (90). This enzyme is known, in other tissues, to preferentially esterify the more unsaturated fatty acids to form lecithin (91). Therefore the specificity of this enzyme may explain the high relative per cent of arachidonic acid in placental tissue. In the *rat* maternal circulating lysolecithin is removed from the circulation by the placenta and esterified to placental lecithin (92). If the lecithin so formed enters the fetal circulation an explanation would be provided for the high relative per cent of fetal lecithin arachidonic acid However in the pregnant *rat* infused with P^{32} labelled lysolecithin no radioactivity is found in the fetus (92). Alternatively if the lecithin formed in the placenta were to release its fatty acid in the fetal side of the syncytial cell, the transport of individual fatty acids as phospholipid esters would be complete. If this cycle occurs there should be measurable lecithinase activity in placental cells. Minimal lecithinase activity is reported in the *rat* placenta (93), but none is found in the human placenta (94). Therefore transport of fatty acids to the fetus as phospholipid esters remains doubtful. These investigations should be extended to the ethanolamine and serine phospholipids.

Phospholipids are synthesized in the placenta as evidenced by the incorporation of P^{32} into all phospholipid fractions in incubations utilizing placental tissue slices. This incorporation is reportedly stimulated by the addition of estradiol to the incubation (95). In placental homogenates of twenty week old placentas, as contrasted to term placentas, no phospholipid is synthesized from C acetate (96). In the *rat* the incorporation of P^{32} into lecithin, lysolecithin, and phosphatidyl ethanolamine increases markedly as gestation progresses (97) This again suggests a possible dependency on maternal lipids in early pregnancy

It should be mentioned that several authors, studying the transport of amino acids across the *rat* placenta have described a phosphatido-peptide fraction in the placenta which may be involved in this transport (98 99) These findings merit further study

Summary (see Fig. 4). It is probable that intact phospholipids enter the placenta from the maternal circulation but do not pass directly into the fetal circulation. Maternal lysolecithin may well be the precourser of placental lecithin. The fate of lecithin synthesized in the placenta is unknown. The possibility of it acting as a specific fatty acid carrier to the fetal circulation is doubtful since the hydrolysis of lecithin apparently doesn't occur in placental tissue.

CORRELATION OF LIPID METABOLISM TO PERINATAL PHYSIOLOGY

Maternal diseases Toxemia and diabetes, perhaps because of the morphological changes in the placenta, have been repeatedly studied with regard to changes in maternal fetal and placental lipids. In general consistent abnormalities have not been found.

In toxemia changes in maternal lipids (37 100 101 102) placental lipids (3 103 194 105) and fetal lipids (46) have been reported. Other studies report no change (49 106 107) The reported changes are not consistent from report to report and in the most recent analysis the only significant difference is an increase in placental triglycerides which remains unexplained (3) In an excellent review it is pointed out that variables other than the toxemic process may affect lipid levels in toxemia. Among these are the administration of glucose and changes in plasma volume (108) The investigation of placental lipid metabolic routes in abnormal states has hardly begun. Reportedly the synthesis of phospholipids from C^{14} acetate by placental tissue does not occur in severe toxemia (96)

An interesting speculation regarding toxemia is *that the placental release of phosphatidylethanol* amine and phosphatidylserine into the maternal circulation may lead to intravascular coagulation accounting for the lesions seen in the maternal liver kidney and brain (108)

At the present time there is *little indication* of abnormal lipid metabolism or transport occurring in much less causing, toxemia.

In diabetes changes in maternal lipids (109 110) and fetal lipids (109 110 111) have been reported, whereas other studies on the placental lipids (112) newborn adipose tissue lipids (60), and umbilical cord blood free fatty acid levels in prediabetic progeny (49) *are reported as normal* The lack of similar analyses between studies and the relatively small number of samples in most studies make it impossible to draw any conclusions.

There is however one common finding! Diabetic progeny do not respond after birth with as marked an early rise in free fatty acids (10, 36 54) It is suggested that this results from a state of hyperinsulinism in the infant (10) or low levels of growth hormone (113) However no explanation is proven.

Onset of labor In *rabbits*, dipalmitoyl lecithin enhances the frequency and amplitude of uterine contractions (114) Infusions of cephalin are also reported to increase labour activity in humans (115) Another study reports isolating from human placentas a fatty acid (felt to be arachidonate) which stimulates smooth muscle contraction (116) This presumed fatty acid and its *activity is also found in amniotic fluid* (117) These studies give rise to the fascinating speculation that the placental metabolism of arachidonate and its precoursers could be related to the onset of normal or abnormal labor

Perinatal free fatty acid metabolism. In trying to explain the apparent lack of mobilization of free fatty acids in diabetic progeny we are led into the puzzling area of lipid metabolism in the infant before and after birth. It has long been stated that *in utero* the chief source of fetal energy is glucose and that lipids are not catabolized for energy The arguments for this presumption are the low levels of free fatty acids (118), glycerol (50) and ketones (55) at birth as well as the characteristically high respiratory quotient of the newborn (119)

That this is not necessarily the case at all times *in all gestations is suggested by several reports.* The oxidation of octanoic acid to acetoacetate has been demonstrated in the fetal liver (1‿0) and this capability in the placenta of different gestational ages should be investigated. An increase in *umbilical cord blood free fatty acids is described* in fetuses hypoxemic for about six hours as compared to those hypoxemic for about 2 1/ hours before birth (121) An elevation of the fetal/maternal ketone body ratio in the umbilical cord blood of toxemic offspring suggests prenatal fat catabolism (122). If free fatty acids are mobilized and oxidized before birth the question is if they *arise from the fetal adipose tissue or from the placenta.*

Recently it has been suggested that maternal hypoxia decreases the placental transport of glucose (123) When this occurs does the fetus mobilize free fatty acids as an energy source? Presumably in cases of intrauterine growth failure the situation of relative hypoxia and poor placental transport has occurred. At birth hypotrophic infants have low umbilical cord blood glucose levels but normal free fatty acid levels. This is followed by an accentuated free fatty acid rise after birth

(124) This would seem to indicate no free fatty acid mobilization before birth in these cases. Does the fetus respond to stimuli for free fatty acid mobilization? In the fetal *lamb* the free fatty acid response to intravascular infusions of adrenaline is very small and increases gradually after birth (125). From these data it appears that free fatty acid mobilization in the normal fetus is minimal.

After birth, the rise in free fatty acids in normal infants correlates with a fall in blood glucose (46, 126) and may be prevented by glucose administration (126). That this response is mediated by the sympathetic nervous system is suggested in newborn *lambs* since the intravenous injection of hexamethonium inhibits the free fatty acid rise (127).

Lipolysis occurs in infant adipose tissue most rapidly in the first few hours after birth and is least affected by the addition of glucose in the first fifteen hours of life. This factor distinguishes lipolysis in newborn adipose tissue from that process in the more mature infant's adipose tissue (128). Also, measuring the incorporation of C[14] palmitate into newborn adipose triglycerides there is reported not only an elevated level of diglyceride in this tissue but the incorporation of C[14] into that is probably a 1,3 diglyceride not found in adults (129). Obviously more investigation is needed in newborn adipose tissue metabolism.

The normal postpartum rise in the newborn infants free fatty acids is absent in diabetic offspring, as previously mentioned, delayed onset of respiration (46), prenatal maternal-fetal circulatory disturbances in *sheep* (130), and in some premature infants (54). It is suggested that the postnatal change in plasma free fatty acids may provide measure of the total body response to postnatal metabolic demands (130).

The decreased fatty acid response of premature infants (54) and diabetic progeny and the close relation of these two situations to hyaline membrane disease suggest an interesting area of study. If pulmonary surfactant is synthesized utilizing circulating free fatty acids, as is apparently the case in fetal *lambs* (131) and if the amount of surfactant is related to the occurrence of hyaline membrane disease (which is unknown), then a mechanism for the development of this disease is apparent.

No explanations for these variations from normal have been proven. However it does appear that perinatal free fatty acid metabolism may reflect some of the prenatal stresses which are currently so difficult to quantitate. This should be a rewarding area of research.

Prenatal essential fatty acid deficiency. A maternal diet deficient in the essential fatty acids or the inadequate transport of these fatty acids across the placenta could be expected to affect intrauterine growth. In newborn *rats* the birth weight and tissue content of linoleic acid is markedly decreased when the mother is fed a fat deficient diet (13). Also the dermatologic signs of essential fatty acid deficiency occur rapidly if the offspring receive a diet deficient in linoleic acid (133). In human infants demonstrating intrauterine growth failure analyses of placental and fetal tissue lipids are not now available and would be interesting.

SUMMARY

The more recent animal studies reveal the maternal origin of many placental and fetal lipids. In most studies the degree of transport across the placenta and the degree of fetal or placental synthesis of lipids varies with gestational age. Apparently earlier in pregnancy there is more dependence on maternal lipids to provide placental and fetal lipids. In most lipid classes studied the placenta has the capability of altering those lipids presented to it by selective transport and interconversions. Also, most lipid classes are synthesized *de novo* in the placenta.

This review of available information illustrates the many difficulties in describing placental lipid metabolism and transport. The first of these is the extrapolation of data from any other species to man. We hope that increased sophistication in the use of placental perfusion and in the preservation of human placental tissue will lead to the determination of the transport mechanisms in man as well as in other animals. Secondly composition studies are of value only in that they point the direction in which metabolic studies should proceed. The third problem is that the *in vitro* metabolic studies, which tell us what reactions may occur in placental tissue, are not applicable to the *in vivo* situation, since the magnitude of these reactions is unknown. This information can come only from the perfusion of the placenta with the substrates in question. Finally it appears

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that the correlation of placental lipids to maternal fetal disease is not going to be easily shown. Perhaps the best approach is the definition of the functional capacity of the placenta to perform metabolic alterations of certain lipids. Then any alteration in this functional capacity of the placenta might well be more meaningful than an alteration in the lipid pattern of the placenta in disease states. In all the studies to be performed, a great need exists for the determination of composition and metabolic pathways in relationship to the time of gestation. Studies should be done at different periods of gestation for both the metabolism and transport of lipids appears to vary with gestational age

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that the correlation of placental lipids to maternal-fetal disease is not going to be easily shown Perhaps the best approach is the definition of the functional capacity of the placenta to perform metabolic alterations of certain lipids. Then any alteration in this functional capacity of the placenta might well be more meaningful than an alteration in the lipid pattern of the placenta in disease states. In all the studies to be performed, a great need exists for the determination of composition and metabolic pathways in relationship to the time of gestation. Studies should be done at different periods of gestation for both the metabolism and transport of lipids appears to vary with gestational age

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HUMAN GROWTH HORMONE

A METHODOLOGICAL AND CLINICAL STUDY

BY OTTO WESTPHAL

ALMQVIST & WIKSELLS BOKTRYCKERI AB UPPSALA

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From the Department of Paediatrics, University Hospital, Uppsala
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HUMAN GROWTH HORMONE

A Methodological and Clinical Study

by

OTTO WESTPHAL

UPPSALA 1968

To LISBETH,
Susanne and Bengt

The language has been revised by
Mr Robert Johnsen

Statistical advisor
Bernhard Huitfeldt
lecturer of statistics

Ink drawings have been performed by
Birgit Häggquist

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PART I

Radioimmunoassay of Human Growth Hormone

PART II

Clinical study of human growth hormone on children and newborn infants

In the present study special interest has been directed to the chromatoelectrophoretic method described by Glick et al. (1963). This method was originally published for insulin by Berson et al. (1956). Small amounts of HGH are strongly adsorbed on a special paper whilst that bound to antibody moves towards the anode with the gamma globulins. The separation must be carried out at 4° C since the heat generated by the current may cause dissociation of the labeled HGH at higher temperatures. Yalow and Berson (1964) however showed that the flow of buffer along a strip may be effected very simply by evaporation and that method has been used in this study. The method is described in detail and the influence of damage to the labeled HGH has been studied. Special attention is given to the application of the method on neonatal plasma.

CHAPTER I

Introduction

Until recently the assay of hormones in blood was achieved in most instances by bio-assay techniques. A number of bio-assays have been suggested for human growth hormone (HGH) (Evans and Simpson 1931 Marx et al. 1942 and Evans et al 1943) However the specificity and precision of all the biological methods were insufficient for them to be of clinical use. Read and Bryan (1960) adapted the haemagglutination inhibition test for HGH which proved to be satisfactory for the quantitative determination of HGH in highly purified anterior pituitary extracts but was unreliable when applied to human serum because of nonspecific factors in the serum The radioimmunological method for insulin was introduced in 1959 by Berson and Yalow and was applied to HGH independently by Hunter and Greenwood (1962 a) Utiger et al (1962) and Glick et al (1963) The principle of the method depends on the competition between radioactively labeled and unlabeled hormone for the specific binding sites of the antibody (Fig 1) The higher the concentration of the unlabeled hormone the less radioactively labeled hormone will be bound to the antibody After separating the bound from the free hormone the fractions can be measured. Using suitably small, known quantities of unlabeled hormone a standard curve is prepared. The concentration of hormone in unknown samples can be read off the curve directly

In the radioimmunoassay of hormones in blood it is customarily assumed that labeled

Fig 1 Principle of radioimmunoassay

and unlabeled hormones behave identically that the circulating hormone is chemically and immunologically identical with the standard hormone preparation that the amount of hormone bound by the antibody is independent of the concentration of the hormone and that different antisera made against a particular antigen will give a similar quantitative response in the immunoassay system.

The HGH used for immunoassay has been prepared by several different methods (Li and Papkoff 1956 Raben 1959 Roos et al. 1963) and there seems to be some differences in homogeneity between the preparations. It would be more precise to use the term immunoreactive growth hormone for HGH amounts estimated with radioimmunoassays. This term however is inconvenient to use in practice and HGH is substituted in the following for immunoreactive growth hormone.

The various methods available for radioimmunoassay of HGH differ mainly in the technique used to separate free from antibody bound hormone A perfect system would show no labeled antigen in the bound fraction in the absence of antibody and 100 per cent of the labeled antigen in the 'bound' fraction after incubation with excess antibody A number of methods for separation have been published among them by electrophoresis on cellulose acetate membranes, (Hunter and Greenwood 1964) polyacrylamide gel electrophoresis (Fitschen 1964) chromatoelectrophoresis (Glick et al 1963) ion-exchange-resin (Lazarus and Young 1966) adsorption on charcoal (Lau et al 1966) and by using a second antibody to precipitate the antibody bound hormone (Utiger et al. 1962 Hartog et al. 1964 a, Ceraci et al. 1966)

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CHAPTER II

Analytical procedure for a radioimmunoassay of human growth hormone

In collaboration with Paul Roos and
Jan I Thorell

Source of human growth hormone

HGH prepared by the method of Roos et al (1963) was used throughout the study without further purification for immunisation for labeling and as standard HGH. HGH I C.R F batch 6 peak II contributed by Dr F C. Greenwood, London and NIH-GH HS 612 A obtained from Dr A. Wilhelmi, Atlanta Georgia have been used for methodological studies.

During the study six different Roos preparations have been used for immunoassay purposes. For the preparation of the guinea pig antiserum to HGH GF 19 was used. As standard solutions 1963 — 4/1965 GF 25 26 3 were used, later GF 29 2 and for methodological studies, GF 126 For labeling purposes no preparation older than 8 months was used as it was noted that prolonged storage resulted in a decreased yield in the labeling procedure. The following preparations were labeled GF 25 26 3 29 2, 39 2, 48 53 and for methodological studies GF 57 and GF 60 The preparations have been lyophylised and stored at +4°C. Labeled growth hormone was prepared every 3—4 weeks. Before a new batch of growth hormone was used for labeling its immunological activity was compared with the current laboratory standard. Furthermore the old and the new batches were labeled simultaneously to compare the immunological activity of the labeled preparations. No difference could be detected between the preparations except for preparations 57 and 60

Preparation of ^{131}I labeled growth hormone

The modification of Benerjee and Gibson (1962) of the original method by Hunter and Greenwood (1962 b) was used for labeling The carrier free sodium (^{131}I) iodide was used within 36 hours of the commercial preparation A 5μg HGH sample was shaken 60 sec with 2 mC sodium iodide and 30 μg chloramine-T as oxidizing agent. The reaction was stopped by adding 200 μg sodium meta bisulfite. All reagents except ^{131}I were dissolved in buffer 1 For buffer solutions see below

The separation of ^{131}I labeled HGH from the reaction mixture has been modified from the Banerjee-Gibson (1962) method and from that used by Hunter and Greenwood (1962 b) The mixture was passed through a column of Sephadex G 50 (Pharmacia, Uppsala Sweden) the column measuring 1 8 cm in diameter and containing 10 g of dry gel. The gel was allowed to swell in barbital buffer 2 in a beaker for 24 hours before packing of the column. To minimize adsorption onto the gel 100 mg *crystalline serum albumin* was passed through the column followed by a minimum of two column volumes of buffer 2 prior to

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**Ass. Prof Institute of Pathology University of Uppsala, Sweden.

the application of the reaction mixture. The columns were run gravimetrically at a flow rate of approximately 3 ml/5 minutes. Fractions of $1^1/_2$ ml were collected manually. To the fractions 0.05 ml of 7 % bovine serum albumin in buffer 3 was immediately added in order to prevent radiation damage. They were then counted in a well-type scintillation counter (Philips PW 4119) with suitable shielding.

The radioactivity was obtained in 3 peaks (Fig. 2). The approximate yield of labeling was calculated by the relation between the salt peak and the protein containing peaks.

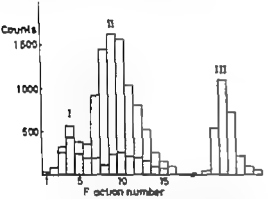

Fig. 2. Gel filtration of reaction mixture of ¹³¹I-labeled growth hormone. Counts are arbitrary radioactive units. ... indicates amount of damaged hormone. The best fractions are in the front part of the second peak. In the experiments fraction 8 was used for immunoassay. Peak III is the radioactive I 131 salt peak.

All fractions were tested for degradation products (damaged HGH) in the following way: 10 µl of gel filtration fractions were mixed with 100 µl of a 7 % bovine serum albumin solution in buffer 2 and 500 µl of buffer 3. Fifty µl of this mixture was applied on a moistened 2×25 cm paper strip (Whatman 3 MC). A minimal amount of Brom Cresol green was dropped at the application line for flow identification. The paper strips were suspended horizontally with one end immersed in buffer 2. Intact HGH is adsorbed at the application line while the degradation products migrate with the carrier proteins in the buffer flow to the center of the paper strip. This modification of the originally chromato-electrophoretic technique of Berson et al (1956) was chosen since it was shown by Yalow and Berson (1964) that the flow of buffer along the strip may be effected very simple by evaporation. If antibody is added the antibody-bound growth hormone and the damaged labeled hormone move together in the buffer flow chromatography as well as in the chromato-electrophoretic system. Flow chromatography was performed at room temperature not exceeding 20 C using cooled buffer 2. The procedure was stopped after about 30 minutes using the front of the Brom Cresol green as indicator for adequate separation. After drying the strips at 120 C they were scanned with a Geiger Müller tube using a slit of 2 mm. The separation is shown in Fig. 3.

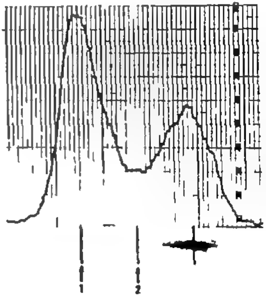

Fig. 3. Buffer flow chromatography on paper strip and the monitored activity.
↑ 1 indicates application site. ↑ 2 indicates line where cutting of the strip was performed. The dark zone is the Brom Cresol dye indicating the fraction that moves with the proteins.

The fractions of damaged HGH in different tubes was calculated. The total fraction of damage (D) during the labeling was cal

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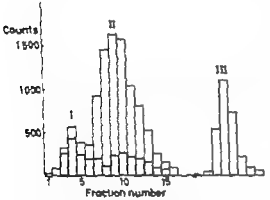

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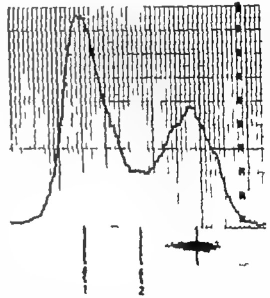

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In collaboration with Paul Roos* and Jan I Thorell**

Source of human growth hormone

HGH prepared by the method of Roos et al (1963) was used throughout the study without further purification for immunisation for labeling and as standard HGH. HGH I C.R.F batch 6 peak II contributed by Dr F C. Greenwood London and NIH GH HS 612 A obtained from Dr A Wilhelmi Atlanta, Georgia have been used for methodological studies.

During the study six different Roos preparations have been used for immunoassay purposes. For the preparation of the guinea pig antiserum to HGH GF 19 was used. As standard solutions 1963 — 4/1965 GF 25 26 3 were used, later GF 29 2 and for methodological studies, GF 126. For labeling purposes *no preparation older than 8 months was used,* as it was noted that prolonged storage resulted in a decreased yield in the labeling procedure. The following preparations were labeled GF 25 26 3, 29 2, 39 2, 48, 53 and for methodological studies GF 57 and GF 60. The preparations have been lyophylised and stored at +4 C. Labeled growth hormone *was prepared every 3—4 weeks. Before a new* batch of growth hormone was used for labeling its immunological activity was compared with the current laboratory standard. Furthermore the old and the new batches were labeled simultaneously to compare the immunological activity of the labeled preparations. No difference could be detected between the preparations except for preparations 57 and 60.

Preparation of ^{131}I labeled growth hormone

The modification of Benerjee and Gibson (1962) of the original method by Hunter and *Greenwood (1962 b) was used for labeling.* The carrier free sodium (^{131}I) iodide was used within 36 hours of the commercial preparation. A 5 µg HGH sample was shaken 60 sec with 2 mC sodium iodide and 30 µg chloramine-T as oxidizing agent. The reaction was stopped by adding 200 µg sodium meta bisulfite. All reagents except ^{131}I were *dissolved in buffer 1. For buffer solutions see* below.

The separation of ^{131}I labeled HGH from the reaction mixture has been modified from the Banerjee-Gibson (1962) method and from that used by Hunter and Greenwood (1962 b). The mixture was passed through a column of Sephadex G-50 (Pharmacia, Uppsala, Sweden) *the column measuring* 1.8 cm in diameter and containing 10 g of dry gel. The gel was allowed to swell in barbital buffer 2 in a beaker for 24 hours *before packing of the* column. To minimize adsorption onto the gel 100 mg crystalline serum albumin was passed through the column followed by a minimum of two column volumes of buffer 2 prior to

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2. 50 µl plasma or various amounts of HGH-standard giving final concentrations of 0.1, 2, 10, 20, 50 and 100 ng HGH/ml.
3. Guinea pig antiserum to HGH, final dilution 1:500.000.
4. Buffer 3 used as diluent to a final incubation volume of 500 µl.

For the standard curve duplicate tubes were prepared for every concentration of standard HGH. For plasma samples triplicate tubes were prepared.

In order to enable calculation of the incubation damage an incubation mixture identical with the standard or unknown plasma sample, but without antibody, was prepared in duplicate for the standard curve and in triplicate for plasma from each patient. If there were more than 3 samples from the same patient the first and last samples were tested. The incubation mixture was mixed carefully after preparation and 24 hours later. It was kept at +4°C for 4 days.

Separation of free and antibody bound HGH

To every tube for the standard curve 50 µl of adult heparin plasma (from blood donors) was added as carrier protein. To the plasma samples 50 µl buffer 3 was added to keep identical volumes. After moderate shaking 2×125 µl was put on a 4×25 cm paper strip of Whatman 3 MC paper previously moistened with buffer 2. On the application site a minimal amount of Brom Cresol green was added as indicator. Flow chromatography was then performed at room temperature not exceeding 20 C, using buffer 2 that was kept at 4 C by adding pieces of the frozen buffer. The procedure was identical with that described for testing the labeled HGH fractions. The chromatography was stopped when the front had moved exactly 6 cm (after about 30 min.). This gave an adequate separation between the free HGH that was adsorbed at the application site and the antibody-bound HGH that moved with the protein. The strips were dried at 120 C and cut in two parts between application site and the moving proteins and the radioactivity measured. The control tubes (incubation mixture without antibody) were handled identically.

Calculation of standard curve

By this method it is possible to make an approximate correction for damaged HGH which in the buffer flow system moves with the protein and the antibody-bound HGH but has no antibody binding capacity. The calculation is made on the control samples (incubation mixture without antibody). If I is intact HGH measured at the application line and M is damaged HGH moving with the protein and the per cent damaged is K than $K = \frac{M}{M+I} \times 100$

The true $\frac{B}{B+F}$ ratio of a sample is, if F is the free HGH measured at the application point and B_t is antibody-bound and damaged HGH moving with the proteins

$$\frac{B - K\ (B_t+F)}{F+B - K\ (B_t+F)}$$

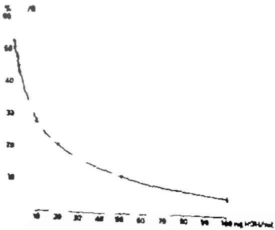

Fig. 4. Mean and S.D. of 10 consecutive standard curves plotted in linear diagram. Bar indicate S.D.

culated in the following way d = sum of counts of damaged HGH in all tubes with more than 100 counts in peaks I and II (Shadowed area in Fig 2) T = sum of counts in all tubes with more than 100 counts in peak I and II $D = \frac{d}{T} \times 100$ The total damaged fraction D was usually about 25 %. The tube with the least fraction of damage was used for the assay It was diluted in buffer 3 to a concentration of 10 ng/ml and kept at —20°C.

Human growth hormone standard

During the period 1963 to April 1965 a standard solution was prepared from Roos GF 25 26 3 Stock solutions in concentrations 1 10 and 50 ng/ml in buffer 3 were prepared and kept at —70°C. The amount sufficient for one month s use was kept at —20°C. An accident with the main part of the standard solutions made it necessary to prepare a new standard A freshly prepared Roos HGH GF 29 2 was diluted and stored as above Very careful tests with repeated standard curves could not reveal any differences in the immunological activity of the two preparations.

Guinea pig antiserum to HGH

Adult guinea pigs were injected subcutaneously three times with 1 mg of Roos GF 19 in Freunds complete adjuvant. The intervals between the injections were three weeks, the guinea pigs were bled by cardiac puncture one week after the last injection The serum and stock dilutions were kept at —70 C, amounts for one month s use, at — 20°C. Antiserum Ma 1 was used throughout the study This antiserum in antibody excess proportions completely bound ^{131}I HGH. The binding was fully prevented if the antibodies were saturated with unlabeled HGH.

Buffer solutions

1 For preparation of ^{131}I HGH 0.16 M borate buffer pH 8 0 2 For gel filtration and buffer flow chromatography 0 1 M Barbital buffer (LKB 3276) pH 8 6 3 For dilution of antibody and ^{131}I HGH for HGH standard solutions and as incubation diluent 0 1 M Barbital buffer (LKB 3276) with 0 25 % crystalline bovine serum albumin

Reagents and equipment

Indicator for buffer flow indentification 2 ml 0 1 M Barbital buffer (LKB 3276) pH 8 6 with 7 % crystalline bovine serum albumin and 2—3 grains of Brom Cresol green (Tetra brom-m-cresolsulfonephthalein)

Albumin Crystalline bovine serum albumin (BSA) was a gift from AB Kabi, Stockholm Sweden It was prepared by Armour and Co Eastbourne Sussex, England.

^{131}Iodide Sodium ^{131}I carrier free (IBS3) The Radiochemical Centre, Amersham England.

Pipettes For pipetting labeled HGH HGH antibody and plasma into incubation tubes Hamilton microliter syringes with 100 µl capacity and 5 cm cemented needle and Chaney Adaptation (710—NCH) from Hamilton Company Whitteer Calif USA For HGH standards AGLA brand Micrometer Syringe Outfit from Burroughs Wellcome & Co London England.

Chromatography paper Whatman 3 MC. Two different batches without significant differences were used throughout the study (Four of six tested batches were not suitable)

Counting equipment Philips PW 4119 well type scintillation counter and Baird Atomic automatic sample changer

Incubation mixture

In a 5.5×1 0 glass tube a mixture of

1 0.2 ng ^{131}I HGH.

2. 50 µl plasma or various amounts of HGH-standard giving final concentrations of 0.1, 2, 10, 20, 50 and 100 ng HGH/ml.
3. Guinea pig antiserum to HGH, final dilution 1:500.000.
4. Buffer 3 used as diluent to a final incubation volume of 500 µl.

For the standard curve duplicate tubes were prepared for every concentration of standard HGH. For plasma samples triplicate tubes were prepared.

In order to enable calculation of the incubation damage an incubation mixture identical with the standard or unknown plasma sample, but without antibody, was prepared in duplicate for the standard curve and in triplicate for plasma from each patient. If there were more than 3 samples from the same patient the first and last samples were tested. The incubation mixture was mixed carefully after preparation and 24 hours later. It was kept at +4° C for 4 days.

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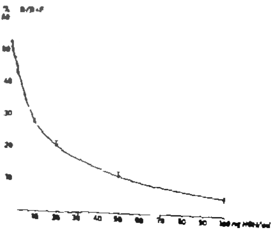

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Chromatography paper Whatman 3 MC. Two different batches without significant differences were used throughout the study (Four of six tested batches were not suitable)

Counting equipment Philips PW 4119 well type scintillation counter and Baird Atomic automatic sample changer

Incubation mixture

In a 5.5×1 0 glass tube a mixture of
1 0 2 ng ^{131}I HGH

2. 50 µl plasma or various amounts of HGH-standard giving final concentrations of 0.1, 2, 10, 20, 50 and 100 ng HGH/ml.
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4. Buffer 3 used as diluent to a final incubation volume of 500 µl.

For the standard curve duplicate tubes were prepared for every concentration of standard HGH. For plasma samples triplicate tubes were prepared.

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Calculation of standard curve

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The true $\frac{B}{B+F}$ ratio of a sample is, if F is the free HGH measured at the application point and B_1 is antibody-bound and damaged HGH moving with the proteins:

$$\frac{B_1 - K\ (B+F)}{F + B_1 - K\ (B_1+F)}$$

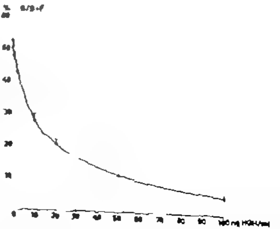


Fig. 4. Mean and S.D. of 10 consecutive standard curve plotted in linear diagram. Bars indicate S.D.

K varies between 10—30 % and if 35 % or more the precision of the method is markedly diminished In the standard curve the true $\frac{B}{B+F}$ ratio is expressed in per cent. The standard curve can be plotted in a linear system with per cent $\frac{B}{B+F}$ on the ordinate and the HGH concentrations on the abscissa, (Fig 4) It is, however more convenient to plot the curve in a semilogarithmic diagram (Fig 5) since the curve is nearly linear between 2 and 100 ng HGH/ml.

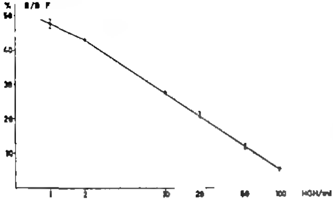


Fig 5 Mean and S.D of 10 consecutive standard curves plotted in a semilogarithmic diagram Bars indicate S D

Calculation of test sample

This was performed in the same way as the standards and the $\frac{B}{B+F}$ ratio was compared with the standard curve, plotted in the semilogarithmic system.

A standard curve and 25—35 test samples in triplicate and with controls as above can be analysed in one series. The laboratory routine was to prepare samples and run buffer flow chromatography twice a week

Methodological studies of the immunoassay for HGH

Effect of different HGH preparations as standard HGH

All HGH preparations used for assay routine are prepared by the method described by Roos et al. (1963) The preparations used are stated in chapter II. So far however no international standard preparation of HGH for immunoassay purpose is available. To compare the laboratory standard with other preparations the following experiments were performed. (November 1966)

HGH preparations studied were

1 Roos GF 6 prepared 1962 and kept lyophylised at +4 C.

2. Roos GF 29 2 our laboratory standard for immunoassay Stock solutions in buffer 3 and in concentration 1 10 and 50 ng/ml were prepared within a month after the preparation of the hormone and kept at —70 C No previously thawed samples were used as standards in these experiments.

3 A British HGH preparation (Imperial Cancer Research Fund batch 6 peak II) contributed by Dr F C. Greenwood. This sample was prepared 1964 and, since December 1964 was kept dissolved in buffer 3 and stored as Roos GF 29 2.

4 A lyophylised Wilhelmi preparation NIH —GH—HS 612 A.

The lyophylised preparations were dissolved in barbital buffer 3 one week before the experiment. The results are shown in Fig 6

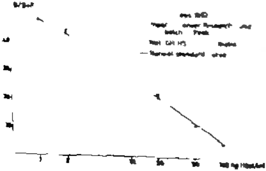


Fig 6 Standard curves with different HGH preparations

The Roos HGH consists of at least four different components when separated on column electrophoresis as shown in Fig. 7

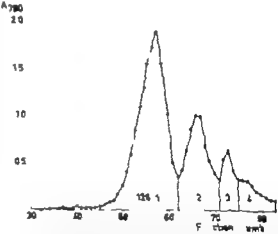


Fig. 7 Protein distribution from column electrophoresis at pH 8.6 of HGH obtained through gel filtration on Sephadex G-100.

These components have identical biological activity (Roos et al. 1963) and similar lactotrophic activity (Lions et al. 1966) The immunological activity of the four components has been studied in a second experiment. The fractions 126 1—4 were components of GF 29 2. The results in Fig. 8 indicate that fraction 126—4 which constitutes a minor

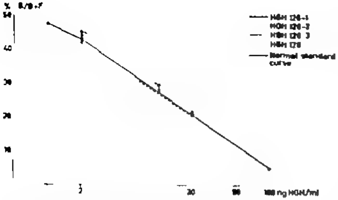


Fig 8 Immunological activity of four different electrophoretic components of GF 29 compared with normal standard curve of GF 29

portion has an immunological activity markedly lower than the other components.

From the first experiment it can be concluded that the HGH assay of a given sample can differ if compared with different standard preparations. The immunological activity of our laboratory standard is higher than the preparation used by Greenwood and slightly higher than the Wilhelmi preparation. From this it follows that our HGH values will be lower than those published by authors using one of the above mentioned preparations as standards This indicates the necessity of an international standard for HGH used for immunoassay The markedly low immunological activity of GF 6 (Fig 6) might be the result of the storage of the preparation but might even indicate that earlier Roos preparations were less active

The second experiment shows that available "clean growth hormone easily can be fractionated into different components and despite the fact that these components have identical biological activity the immunological activity varies From this it can be concluded that the immunological and biological sites of the HGH molecule are not completely identical Thus HGH preparations intended for clinical purposes must be tested not only for their immunological activity but for their biological activity as well

Separation of ^{131}I labeled HGH from reaction mixture

Initially the method of Hunter and Greenwood (1962 b) was tested The radioactivity was monitored in two peaks, the protein peak and the salt peak There was no apparent difference in the amount of degradation damage in the different tubes of the protein peak and since the degradation damage often exceeded 30 % a more proper separation was necessary Gelfiltration was chosen as a very mild method. Different amounts (2.1—17.5 g) of Sephadex G-50 and G-75 were tried in 1 8 cm diameter columns. The reaction mixture was diluted to a total volume of 2 ml and 0 5 ml was used for every column. The Sephadex used was allowed to swell in buffer 2 in a beaker for 24 hours, and following packing of the column 10 mg crystalline serum albumin per gram Sephadex in buffer 2 was run through the column to prevent adsorption of labeled protein. A minimum of two column volumes of buffer 2 was passed through the columns prior to the application of the reaction mixture. All columns were run gravimetrically the fractions were collected manually in volumes of 1.5 ml The results obtained in 2 different labeling procedures are shown in Table I

As seen in Fig. 9 a double protein peak is seen when 10 g or more of Sephadex G-50

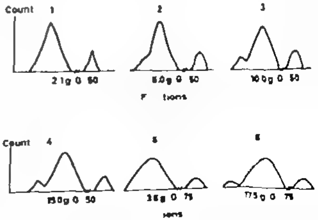


Fig 9 Approximate separation of labeling mixture by gel filtration on varying amounts of G 50 and G-75

TABLE I *Effect of variations in Sephadex separation of reaction mixture*

Mode of separation	Lengt of column in cm	Per cent damaged in best tube	Recovery of reaction mixture	Labeling
Sephadex G-50 2.1 g	10	27	[illegible] %	
Sephadex G-50 5 g	23	22	[illegible] %	1
Sephadex G-50 10 g	46	12	78 %	
Sephadex G-50 15 g	70	11	78 %	
Sephadex G-50 2.1 g	10	29	[illegible] %	
Sephadex G-50 10 g	46	12	77 %	2
Sephadex G-75 3.6 g	7	50	[illegible] %	
Sephadex G-75 17.5 g	35	19	79 %	

is used. There was no advantage in using more than 10 g G-50 or using G-75. The separation with 10 g G-50 was chosen, usually giving a labeled product with less than 15 % degradation damage in the best tube.

Some factors influencing the degradation damage

The problem of degradation products has been deal with by several authors (Yalow and Berson, 1964, Midgley 1966 and Glover et al. 1967) and is one of the main difficulties in the labeling procedure.

In our laboratory as in others the labeling procedure has failed in periods, the only variable being a new preparation of ^{131}I. Generally a bad labeling was characterized by a poor yield (less than 40 %) and a large amount of degradation products. Such preparations could not be used for assay purposes. It was early experienced that the ^{131}I had to be freshly prepared, thus it was normally used within 24 hours after the commercial preparation, and never later than 36 hours after the preparation.

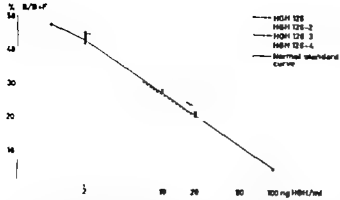
For routine labeling lyophylised Roos GF 25, 26.3, 29.2, 39.2, 48 and 53 were used. No significant differences could be shown between the preparations used for the assay. The yield of the labeling procedure was usually between 60—90 % giving a specific activity of 240—330 μc/μg, the preparation containing less than 1 atom of iodide per molecule HGH.

Since the problem of degradation damage is more pronounced for HGH than for other polypeptide hormones it is conceivable that the HGH molecule is more susceptible than other polypeptides. However HGH is more heterogeneous than other hormones (Hunter 1965, Berson and Yalow 1966, Trygstad 1967). The heterogeneity of the Roos preparation has already been demonstrated (Fig 7). Furthermore it has been shown that lyophylising Roos preparations gives rise to further heterogeneity which may be due to polymerization (Hanston et al. 1966).

To determine whether differences in the storage conditions of Roos HGH alters the labeling product two different batches of HGH prepared by the same procedure were labeled. In one experiment a lyophylised and a frozen (in buffer 1) preparation of GF 57 were labeled simultaneously. In a second experiment GF 57 lyophylised and GF 60 never lyophylised nor frozen were labeled. The results are listed in Table II. The

TABLE II
Effect of storage of HGH on labeling

Preparation	Per cent yield of labeling	Sum of damaged in % of total protein (D)
GF 57 lyophylised	68	21.8
GF 57 frozen	60	18.1
GF 57 lyophylised	70	20.3
GF 60	65	12.3



F g 8 Immunological activity of four different elec trophoretic components of GF 29 compared with nor m l stand d curve of GF 29

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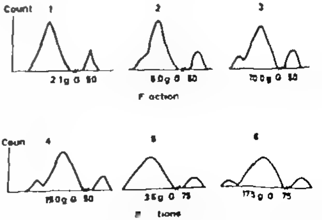

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For routine labeling lyophylised Roos GF 25 26:3 29 2, 39 2 48 and 53 were used. No significant differences could be shown between the preparations used for the assay The yield of the labeling procedure was usually between 60—90 % giving a specific activity of 240—330 μc/μg, the preparation containing less than 1 atom of iodide per molecule HGH.

Since the problem of degradation damage is more pronounced for HGH than for other polypeptide hormones it is conceivable that the HGH molecule is more susceptible than other polypeptides. However HGH is more heterogeneous than other hormones (Hunter 1965 Berson and Yalow 1966, Trygstad 1967) The heterogeneity of the Roos preparation has already been demonstrated (Fig 7) Furthermore it has been shown that lyophylising Roos preparations gives rise to further heterogeneity which may be due to polymerization (Hansson et al. 1966)

To determine whether differences in the storage conditions of Roos HGH alters the labeling product two different batches of HGH prepared by the same procedure were labeled. In one experiment a lyophylised and a frozen (in buffer 1) preparation of GF 57 were labeled simultaneously In a second experiment GF 57 lyophylised and GF 60 never lyophylised nor frozen were labeled. The results are listed in Table II. The

TABLE II
Effect of storage of HGH on labeling

Preparation	Per cent yield of labeling	Sum of damaged in / of total protein (D)
GF 57 lyophylised	68	21.8
GF 57 frozen	60	18.1
GF 57 lyophylised	70	20 3
GF 60	65	12.3

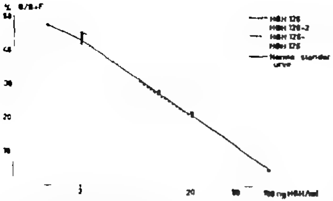

Fig 8 Immunological activity of four different electrophoretic components of GF 29 compared with normal standard curve of GF 29

portion has an immunological activity markedly lower than the other components

From the first experiment it can be concluded that the HGH assay of a given sample can differ if compared with different standard preparations The immunological activity of our laboratory standard is higher than the preparation used by Greenwood and slightly higher than the Wilhelmi preparation. From this it follows that our HGH values will be lower than those published by authors using one of the above mentioned preparations as standards. This indicates the necessity of an international standard for HGH used for immunoassay The markedly low immunological activity of GF 6 (Fig 6) might be the result of the storage of the preparation but might even indicate that earlier Roos preparations were less active

The second experiment shows that available "clean" growth hormone easily can be fractionated into different components and despite the fact that these components have identical biological activity the immunological activity varies. From this it can be concluded that the immunological and biological sites of the HGH molecule are not completely identical. Thus HGH preparations intended for clinical purposes must be tested not only for their immunological activity but for their biological activity as well

Separation of ^{131}I labeled HGH from reaction mixture

Initially the method of Hunter and Greenwood (1962 b) was tested. The radioactivity was monitored in two peaks the protein peak and the salt peak There was no apparent difference in the amount of degradation damage in the different tubes of the protein peak and since the degradation damage often exceeded 30 % a more proper separation was necessary Gelfiltration was chosen as a very mild method. Different amounts (2.1—17.5 g) of Sephadex G-50 and G-75 were tried in 1 8 cm diameter columns. The reaction mixture was diluted to a total volume of 2 ml and 0.5 ml was used for every column. The Sephadex used was allowed to swell in buffer 2 in a beaker for 24 hours, and following packing of the column 10 mg crystalline serum albumin per gram Sephadex in buffer 2 was run through the column to prevent adsorption of labeled protein A minimum of two column volumes of buffer 2 was passed through the columns prior to the application of the reaction mixture. All columns were run gravimetrically the fractions were collected manually in volumes of 1.5 ml. The results obtained in 2 different labeling procedures are shown in Table I

As seen in Fig. 9 a double protein peak is seen when 10 g or more of Sephadex G-50

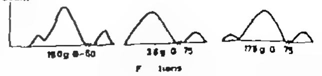

Fig 9 Approximate separation of labeling mixture by gel filtration on varying amount of G-50 and G-75

TABLE I *Effect of variations in Sephadex separation of reaction mixture*

Mode of separation	Length of column in cm	Per cent damaged in best tube	Recovery of reaction mixtur	Labeling
Sephadex G-50 2.1 g	10	27	81 %	1
Sephadex G-50 5 g	23	22	80 %	
Sephadex G-50 10 g	46	12	78 %	
Sephadex G-50 15 g	70	11	78 %	
Sephadex G-50 2.1 g	10	29	79 %	2
Sephadex G-50 10 g	46	12	77 %	
Sephadex G-75 3.6 g	7	30	83	
Sephadex G-75 17.5 g	35	19	79 %	

is used. There was no advantage in using more than 10 g G-50 or using G-75. The separation with 10 g G-50 was chosen, usually giving a labeled product with less than 15 % degradation damage in the best tube.

Some factors influencing the degradation damage

The problem of degradation products has been dealt with by several authors (Yalow and Berson, 1964 Midgley 1966 and Glover et al. 1967) and is one of the main difficulties in the labeling procedure.

In our laboratory as in others the labeling procedure has failed in periods, the only variable being a new preparation of ^{131}I. Generally a bad labeling was characterized by a poor yield (less than 40 %) and a large amount of degradation products. Such preparations could not be used for assay purposes. It was early experienced that the ^{131}I had to be freshly prepared, thus it was normally used within 24 hours after the commercial preparation, and never later than 36 hours after the preparation.

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Testing of antisera

Four different antisera were prepared simultaneously by the procedure described earlier They were tested in the following way Fifty µl of labeled HGH with a calculated concentration of 10 ng/ml was incubated with the antisera in final dilution of 1 10 000 1 100 000 1 250 000 1 500 000 1 1 000 000 and 1 1 500 000 the total volume being 500 µl The dilution giving a $\frac{B}{B+F}$ ratio of 50 % was chosen for mixing a standard curve with standard HGH amounts corresponding to 2 10 50 and 100 ng/ml. The standard curves showed almost identical slopes except for Ma 3 Fig 10 For immunoassay purposes and throughout this study antiserum Ma 1 in final dilution 1 500 000 was used.

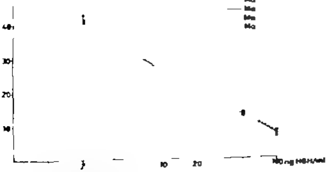
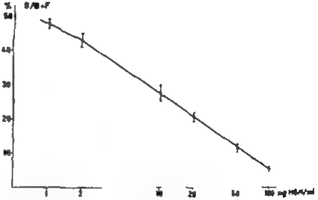


Fig 10 Standard curves determined for 4 different guinea pig antisera.

Effect of different concentrations of unlabeled HGH on the binding of labeled HGH (standard curve)

Fig 11 shows the mean and S D of ten consecutive standard curves plotted in a semilogarithmic diagram. Since the standard curve is very nearly linear between 2—100 ng/ml HGH it is very convenient to use this system



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Effect of different amounts of labeled HGH

The $\frac{B}{B+F}$ ratio will increase if the amount of labeled HGH is decreased. (Fig 12) However since very small amounts of labeled hormone make the counting procedure inconvenient that amount of labeled HGH giving a B/B+F ratio of 50—55 % with the antiserum in final dilution 1 500 000 has been used for routine assays This has been checked on every freshly labeled hormone by incubating a standard curve with 4 different amounts of ^{131}I HGH as shown in Fig 13 For routine assays it gives a sufficient sensivity and a convenient number of counts.

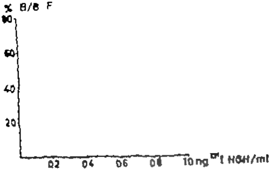

Fig. 12. B/B+F ratio without added standard HGH but various amounts of labeled hormone. Incubation time four days.

It is possible to increase the sensitivity of the assay by reducing the amount of labeled hormone, antiserum and consequently of standards. In a more diluted system however the equilibration time for the antigen-antibody reaction increases. If incubation time exceeds 7 days it is inconvenient. For special purposes however a more sensitive as well as a less sensitive system was prepared, Fig. 14.

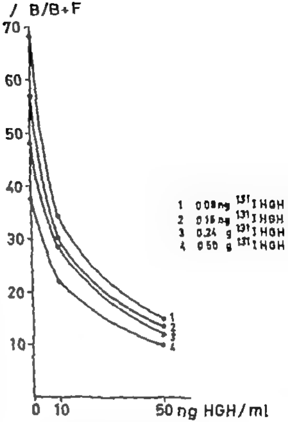

Fig. 13. Standard curves with various amounts of ^{131}I HGH. Dilutions as shown in the figure were made on every freshly labeled ^{131}I HGH preparation. The amounts giving B/B+F ratio of 30—35 % was used for the assay.

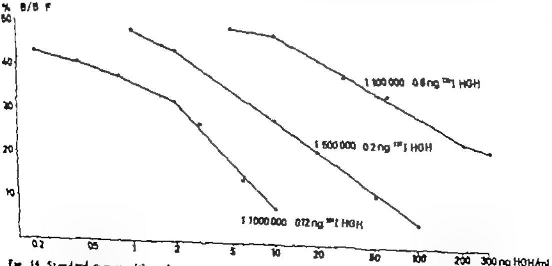

Fig. 14. Standard curves with various sensitivities of the assay. The concentrations of antiser were final dilutions 1:100 000, 1:100 000 and 1:1 000 000. The corresponding amounts of ^{131}I HGH were 0.8, 0.2 and 0.12 ng respectively. Incubation time was 3, 4 and 7 days respectively.

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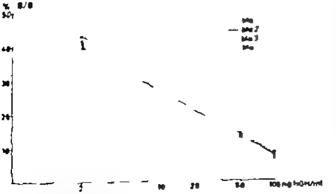

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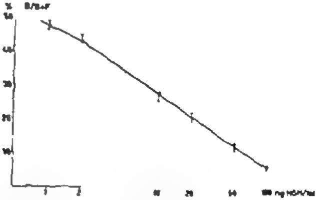

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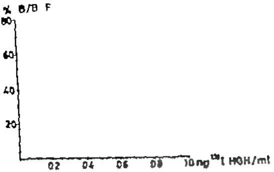
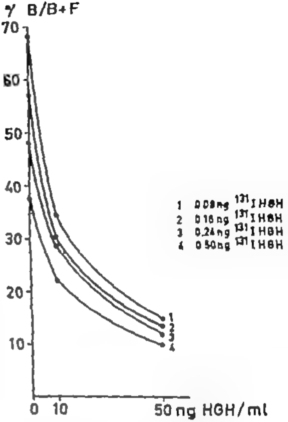


Fig 12. B/B+F ratio without added standard HGH but various amounts of labeled hormone. Incubation time four day



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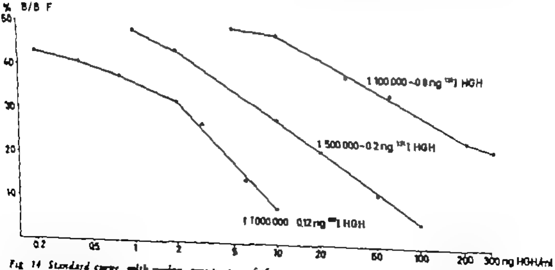

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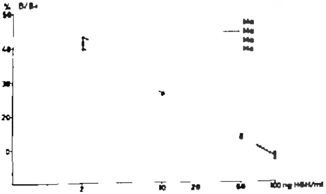

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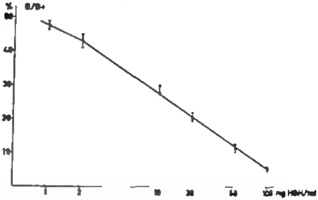

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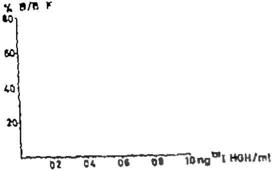

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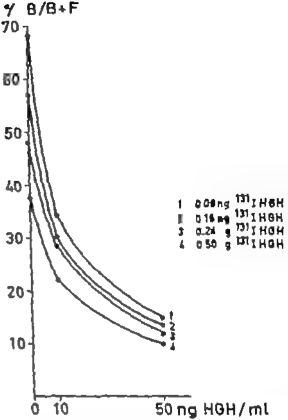

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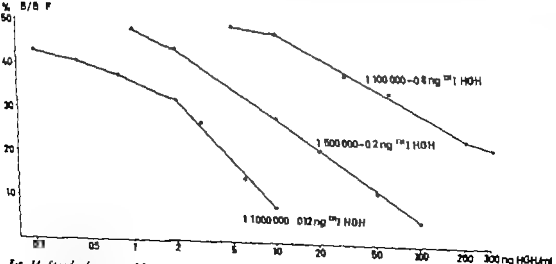

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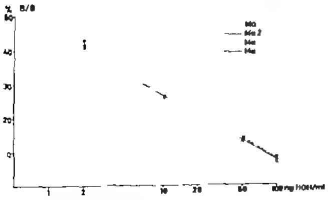

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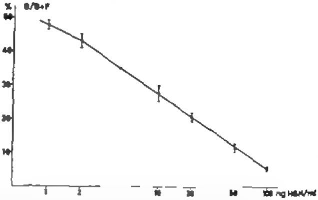

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Effect of degradation damage on standard curve

The precision of the radio-immunoassay decreases as the amount of damaged hormone increases (Berson et al. 1964) Since the amount of damage increases with prolonged storage or by storage of the labeled hormone at room temperature (Berson and Yalow 1966) four standard curves were run simultaneously with the same labeled hormone, the hormone being stored in different ways. The results are shown in Table III

Furthermore, three samples of the same HGH preparation (GF 39 2) were labeled on separate occasions and measured when one was one, another four and the third six weeks old. The preparations were kept at —20 C and had not been thawed prior to the experiment. The results are shown in Fig. 18

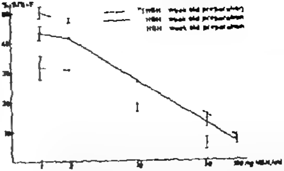


Fig. 18 Labeled HGH GF 39.2 from different labeling and with approximately the same amount of damage at time of preparation The preparations contained degradation damage of 17 %, 56.5 % and 49 % respectively at the time of the experiment. Bars indicate S D

TABLE III. *Effect of storage of labeled HGH*

Storage of preparation GF 39	Incubation damage	Per cent B/B+F ±S.D for various amounts of standard HGH 1 ng/ml	2 ng/ml	10 ng/ml	50 ng/ml
Frozen	19 %	49±2.2	44±2.1	28±1.8	12 ±0.8
+4°C 24 hours	22 %	48±2.0	43±2.7	27±1.5	11.9±0.9
20°C 6 hours	30 %	46±2.6	41±2.7	26±1.9	10.8±1.2
20°C 24 hours	46	38±3.9	36±3.7	23±2.7	8.7±2.1

Both experiments show that the slope of the standard curve is diminished when the damaged fraction increases and that will decrease the precision and consequently increase the S.D For assay purpose labeled hormone with a degradation fraction greater than 35 % has not been used. The labeling procedure was repeated every third or fourth week. The labeled hormone was kept at —20 C, it was thawed in a refrigerator at +4 C and was kept in an ice water bath during the mixing procedure. The incubation mixture was kept at +4 C until it was put on the paper strips for chromatography

Further effects of temperature on the assay

During early experiments with the assay duplicates of the standard curve and triplicates of plasma samples showed a significant difference between comparable samples. It was also noted that on those occasions the time of the buffer flow chromatography was prolonged and the variation between comparable strips pronounced. This effect increased during the day when the buffer used for the flow chromatography assumed room temperature. Since there was no sign of increase in degradation damage it was presumed that

Comparison between standard HGH and labeled HGH

On several occasions during the study the standard curve was compared with another obtained when labeled HGH was used as a standard. Fig 15 shows no significant differences in the immunological behaviour of the two standards

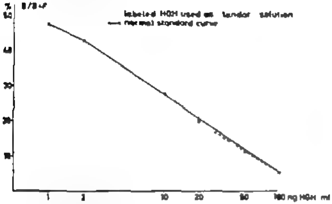


Fig 15 Standard curves with laboratory standard GF 29 2 and with labeled GF 39 2

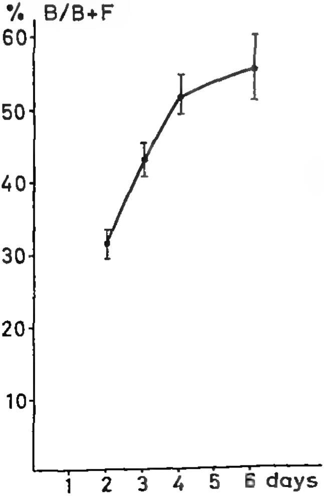


Fig 16. Effect of incubation time Bars indicate S.D

Effect of incubation time on binding of labeled HGH

For this experiment GF 29 2 was used for labeling. The amount of ^{131}I HGH was 0 15 ng/500 μl incubation mixture. Incubation periods of 2 3 4 and 6 days were studied and the results are given in Fig 16 No equilibrium in binding occurred during this period but the difference between four and six days was almost negligible. The S.D was greater in the six day incubated sample. The reason for this was an increase in the incubation damage. For the assay an incubation time of 4 days was routine

Effect of protein on standard curve

Differences in the effect of plasma on the assay have been published Hunter and Greenwood (1964) have stated that if plasma is diluted 1 5 or more no unspecific binding will occur while Cerasi et al (1966) show an unspecific binding in their double antibody assay For this purpose three different standard curves were mixed

1 Ordinary standard curve without protein during incubation.
2. Standard curve incubated with 50 μl of 7 % crystalline bovine serum albumin in barbital buffer 2.
3 Standard curve with 50 μl of heparinized bovine plasma.

As shown in Fig 17 no significant differences are noticable. Thus it is not necessary to incubate the standard curve with protein.

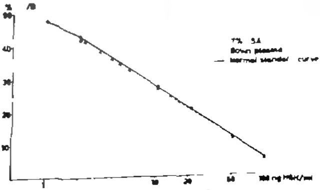


Fig 17 Effect of protein in incubation mixture on standard curves Incubation time four days

Effect of degradation damage on standard curve

The precision of the radio-immunoassay decreases as the amount of damaged hormone increases (Berson et al. 1964). Since the amount of damage increases with prolonged storage or by storage of the labeled hormone at room temperature (Berson and Yalow 1966) four standard curves were run simultaneously with the same labeled hormone, the hormone being stored in different ways. The results are shown in Table III.

Furthermore, three samples of the same HGH preparation (GF 39:2) were labeled on separate occasions and measured when one was one, another four and the third six weeks old. The preparations were kept at −20 C and had not been thawed prior to the experiment. The results are shown in Fig. 18.

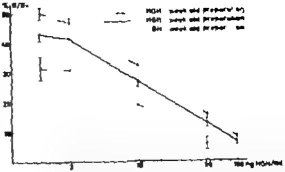


Fig. 18. Labeled HGH GF 39:2 from different labeling and with approximately the same amount of damage at time of preparation. The preparation contained degradation damage of 17 %, 36.5 % and 49 % respectively at the time of the experiment. Bars indicate S.D.

TABLE III. *Effect of storage of labeled HGH*

Storage of preparation CF 39	Incubation damage	Per cent B/B+F ±S.D. for various amounts of standard HGH 1 ng/ml	2 ng/ml	10 ng/ml	50 ng/ml
Frozen	19 %	49±2.2	44±2.1	28±1.8	12 ±0.8
+4°C 24 hours	22	48±2.0	43±2.7	27±1.5	11.9±0.9
20°C 6 hours	30 %	46±2.6	41±2.7	26±1.9	10.8±1.2
20°C 24 hours	46 %	38±3.9	36±3.7	23±2.7	8.7±2.1

Both experiments show that the slope of the standard curve is diminished when the damaged fraction increases and that will decrease the precision and consequently increase the S.D. For assay purpose labeled hormone with a degradation fraction greater than 35 % has not been used. The labeling procedure was repeated every third or fourth week. The labeled hormone was kept at −20 C, it was thawed in a refrigerator at +4 C and was kept in an ice water bath during the mixing procedure. The incubation mixture was kept at +4 C until it was put on the paper strips for chromatography.

Further effects of temperature on the assay

During early experiments with the assay duplicates of the standard curve and triplicates of plasma samples showed a significant difference between comparable samples. It was also noted that on those occasions the time of the buffer-flow chromatography was prolonged and the variation between comparable strips pronounced. This effect increased during the day when the buffer used for the flow chromatography assumed room temperature. Since there was no sign of increase in degradation damage it was presumed that

Comparison between standard HGH and labeled HGH

On several occasions during the study the standard curve was compared with another obtained when labeled HGH was used as a standard Fig 15 shows no significant differ ences in the immunological behaviour of the two standards.

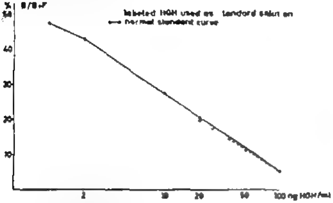
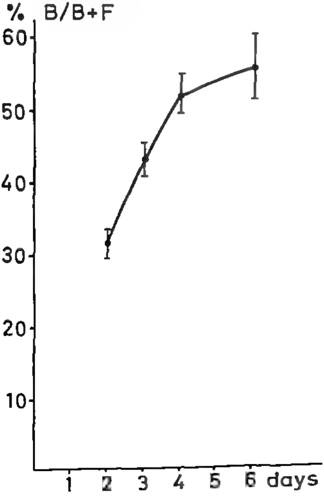


Fig 15 Standard curves with laboratory standard GF 29 2 and with labeled GF 39 2



F g 16 Effect f incubation tim Bars indicate S.D

Effect of incubation time on binding of labeled HGH

For this experiment GF 29 2 was used for labeling The amount of ^{131}I HGH was 0 15 ng/500 µl incubation mixture. Incubation periods of 2 3 4 and 6 days were studied and the results are given in Fig 16 No equilibrium in binding occurred during this period but the difference between four and six days was almost negligible. The S.D was greater in the six day incubated sample. The reason for this was an increase in the incubation damage. For the assay an incuba tion time of 4 days was routine.

Effect of protein on standard curve

Differences in the effect of plasma on the assay have been published. Hunter and Green wood (1964) have stated that if plasma is diluted 1 5 or more no unspecific binding will occur while Cerasi et al. (1966) show an unspecific binding in their double anti body assay For this purpose three different standard curves were mixed.

1 Ordinary standard curve without protein during incubation
2 Standard curve incubated with 50 µl of *7 % crystalline bovine serum albumin in barbital buffer 2*
3 Standard curve with 50 µl of heparinized bovine plasma.

As shown in Fig. 17 no significant differ ences are noticable. Thus it is not necessary to incubate the standard curve with protein.

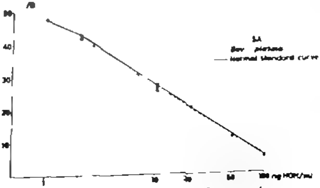


Fig 17 Effect f protein in incubation mixture on standard curves. Incubation time fou days

Application of the method to human plasma with special reference to neonatal plasma

All blood samples were collected in heparinized glass tubes (Vitrum, Stockholm, Sweden) volume 10 ml. If not otherwise stated the assay was performed as follows. A mixture of 0.2 ng ^{131}I HGH, guinea pig antisera to HGH, final dilution 1:500,000, standard HGH in various amounts for incubation of standard curve as described earlier or 50 µl plasma and buffer 3 to a final incubation volume of 500 µl was incubated for 4 days. The samples within one experiment are all run in the same series if not otherwise stated.

During the whole investigation two pooled samples were run in every series. One pooled sample was obtained prior to exchange transfusion from 3 children 4 days of age. The other pool was fasting blood from 3 healthy children 11 years of age. The estimated values were 33 $\pm$1.8 and 4.2 $\pm$0.8 ng/ml (50 determinations).

Effect of incubation time

The pooled samples were incubated 3, 4 and 6 days, respectively. The results are shown in Table V. Prolonged incubation seems to result in lower measurable concentration of HGH, and greater S.D., the latter due to increased degradation damage.

Effect of amounts of labeled HGH and antisera to HGH

The pooled samples were incubated 4 days with amounts of labeled HGH and antisera as shown in Fig. 14 and compared with corresponding standard curves. The results are shown in Table VI. Differences in the obtained results are not noticeable.

TABLE V. *Effect of incubation-time*

	HGH levels in ng/ml ± S.D. (5 estimations)	
Incubation-time	Neonatal plasma	Adolescent plasma
3 days	35 ± 4.2	3.8 ± 1.0
4 days	33 ± 4.2	3.0 ± 0.9
6 days	30 ± 5.9	2.5 ± 1.7

TABLE VI. *Effect of amounts of labeled HGH and antisera to HGH*

^{131}I HGH / Antisera		HGH levels in ng/ml ± S.D. (5 estimations)	
	Incubationstime	Neonatal plasma	Adolescent plasma
0.8 ng / 1:100,000	3 days	34 ± 4.1	<5 but >0
0.2 ng / 1:500,000	4 days	33 ± 3.8	3.1 ± 0.9
0.12 ng / 1:1,000,000	6 days	>10	3.1 ± 0.8

temperature had a direct influence on the flow chromatography An inadequate difference in temperature between buffer and surroundings presumably gave rise to an irregular rate of evaporation and buffer flow The temperature of the buffer was kept at +4°C with pieces of ice and the room temperature was not allowed to exceed 20°C. With these precautions the flow rate was rather constant and, the S D was diminished.

Cutting the paper strips

Initially the paper strips were monitored with a Geiger Müller tube with a small slit, the surface of the two peaks was calculated by planimetry This very time-consuming procedure was substituted by simply cutting the strips. They were then put in plastic tubes placed in an automatic sample changer and counted. The cutting was performed exactly halfway between the application line and the buffer flow indicator as seen in Fig 3 To test the accuracy of this cutting the two methods were compared by running 100 strips by both methods. The difference never exceeded ±2 % of the B/(B+F) ratio

Effects of other hormones on the assay

To check whether other hormones may influence the assay 50 µl of two concentrations of ACTH pituitary LH pituitary FSH chorionic gonadotrophin and insulin respectively were incubated 4 days with 0.2 ng ^{131}I HGH and HGH antiserum in final dilution 1 500,000 The results are shown in Table IV Only LH of pituitary origin and in high doses has any influence on the assay Probably the available LH preparation contained a small amount of HGH. The B/(B+F) ratio in samples with the other hormones tested did not exceed the B/(B+F) ratio of the standard tubes without any added standard HGH This would have been the case if the available antiserum contained antibodies against the actual hormones.

TABLE IV *Effect of some other hormones on the immunoassay of HGH*

Preparation	Amount ı ng	Apparent amou t of HGH ng/ml
ACTH	50	—
	1000	—
LH**	50	—
	1000	18.3 ± 2.1
FSH	50	—
	1000	—
Chorionic gonadotrophins	50	—
	1000	—
Insulin **	50	—
	1000	—

*Cortrophin, AB Pharmacia, Uppsala, Sweden (Source Porcine pituitaries).
**Kindly prepared by P ul Roos, Ph.D Inst. of Biochemistry Uppsala, Sweden
***Gonadex Leo, Hälsingborg, Sweden. (Source Urine of pregnant women).
****Novo AS Copenhagen, Denmark (Source porcine panchres)

Application of the method to human plasma with special reference to neonatal plasma

All blood samples were collected in heparinized glass tubes (Vitrum, Stockholm, Sweden) volume 10 ml. If not otherwise stated the assay was performed as follows. A mixture of 0.2 ng ^{131}I HGH, guinea pig antisera to HGH, final dilution 1:500 000, standard HGH in various amounts for incubation of standard curve as described earlier or 50 µl plasma and buffer 3 to a final incubation volume of 500 µl was incubated for 4 days. The samples within one experiment are all run in the same series if not otherwise stated.

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4 days	33 ± 4.2	3.0 ± 0.9
6 days	30 ± 5.9	2.5 ± 1.

TABLE VI *Effect of amounts of labeled HGH and antisera to HGH*

^{131}I-HGH / Antisera	Incubationtime	HGH levels in ng/ml ± S.D. (5 estimations) Neonatal plasma	Adolescent plasma
0.8 ng / 1:100 000	3 days	34 ± 4.1	<5 but >0
0.2 ng / 1:500 000	4 days	33 ± 3.8	3.1 ± 0.9
0.12 ng / 1:1.000.000	6 days	>10	3.1 ± 0.8

Effect of storage on frozen plasma

The pooled plasma samples have been stored for a period of more than 2 years at —20°C The values obtained after 5 days 1 month 1 year and 2 years are shown in Table VII When the 5 days and 1 month samples were run the laboratory standard was GF 25 26 3 For the remaining samples the laboratory standard was GF 29 2. No difference in obtained HGH values was noted after 2 years storage at —20°

TABLE VII *Effect of storage of frozen plasma (—20°C)*

Time	HGH levels in ng/ml ± S D (5 estimations) Neonatal plasma	Adolescent plasma
5 days	34 ± 4.2	2.7 ± 0 9
1 month	31 ± 4 0	2.9 ± 1 0
1 year	32 ± 3 8	_4 ± 0.8
2 years	31 ± 4 1	3.2 ± 0 9

Effect of room temperature on whole blood and plasma

Freshly drawn blood samples from a 4 day old infant and from a healthy 11 year old girl were divided into two equal parts. One part was allowed to stand for various lengths of time at room temperature before it was spun down and the plasma separated and frozen The other part was immediately spun and the separated plasma allowed to stand for various lengths of time at room temperature before being frozen The results are shown in Table VIII No noticeable changes are seen in plasma samples if stored 6 hours at room temperature. In whole blood however a decrease in immunoreactive HGH is detectable within one hour in neonatal blood and within 2 hours in adolescent blood So the blood samples are immediately put in a refrigerator or in a beaker with ice and spun down and separated within one hour

TABLE VIII *Effect of room temperature on whole blood and plasma*

	HGH n g/ml plasma Mean ± S.D of 5 estimations			
	Neonatal		Ad lescent	
Time	blood	plasma	blood	plasma
10 min	20.2 ± 0.7	19.2 ± 1 2	3 6 ± 0 3	4 0 ± 0.5
20 min	19 5 ± 0 4	19 4 ± 0 9	3 2 ± 0.9	3 6 ± 0.3
60 min	18 3 ± 0.7	20.1 ± 1.3	4 0 ± 0 7	4 3 ± 0.5
2 hrs	17.2 ± 0 4	20.3 ± 1.2	3 2 ± 0.5	4 2 ± 0.4
4 hrs	16.9 ± 0 7	19 6 ± 1 0	7 ± 0.9	4 1 ± 0.6
6 hrs	16.1 ± 0.8	18.8 ± 0.8	0 ± 0 8	3 9 ± 0.5
14 hrs	13.2 ± 0.9	17 1 ± 0 9	1 6 ± 0.9	3.7 ± 0.4
24 hrs	8.5 ± 1 1	15 5 ± 1 0	1 0 ± 0.7	3 2 ± 0.5
48 hrs	5.2 ± 1 0	13.5 ± 1 1	<0.5	_5 ± 0.6

Effect of freezing and thawing on plasma samples

Tubes containing 0.8 ml of pooled plasma were thawed and frozen various times. All samples were estimated in the same series. The results are shown in Table IX and show no effect of repeated thawing.

TABLE IX. *Effect of thawing and freezing on plasma levels of growth hormone*

Number of freezings	HGH in ng/ml plasma. Mean ±S.D of 5 estimations: Neonatal plasma	Adolescent plasma
1	19.5±2.1	3.2±0.9
2	20.5±1.1	3.2±0.8
5	21.8±1.6	3.7±0.5
10	21.7±1.9	3.4±0.7

Effect of hemolysis on plasma levels of immunoreactive growth hormone

Freshly drawn blood samples, one cord blood, one from a healthy 11 year old child were divided into 2 parts, the major portion was spun, the plasma separated and frozen. The minor part was immediately frozen to receive 100 % hemolysis without adding any substances. Twentyfour hours later the samples were thawed and different amounts of the hemolyzed blood were added to the plasma samples. The degree of hemolysis was measured by the method described by Martinek (1966). Results in Table X show that a fairly high amount of hemolysis is tolerated without interfering with the analysis. Very large amounts however will result in decreasing levels of HGH as well as an increase in S.D. Several explanations for the decrease of estimated immunoreactive HGH values are possible. One possibility is dilution of plasma with the intracellular fluid since the amount of HGH in the cells certainly is lower than in plasma. Furthermore the hemoglobin might act as a blocking agent on labeled HGH, which would simulate a *decrease of* available ^{131}I HGH, and with constant amount of antiserum the B/(B+F) ratio would increase, giving a *lower HGH* value. More probably however the hemoglobin interferes with the buffer-flow chromatography. Hemoglobin moves away from the application line as do other proteins. Probably it is able to carry away some of the antibody free intact ^{131}I HGH. This explanation also accounts for the fact that incubation damage as measured in control samples without antibody increases with increasing amount of hemolysis, giving an increase in S.D.

TABLE X. *Effect of hemolysis on HGH levels*

Per cent hemolysis	HGH in ng/ml plasma. Mean ±S.D of 5 estimations: Neonatal plasma	Adolescent plasma	Per cent hemolysis
0.005	75± 5.2	4.5±1.2	0.004
0.5	72± 4.0	3.7±0.9	0.4
0.8	70± 4.8	4.8±0.8	0.8
2.4	72± 5.2	4.0±1.3	2.3
10	68± 6.8	2.7±1.9	9.8
65	56±10.2	1.5±2.0	60
100	32±15.1	<1.0±2.0	100

Effect of storage on frozen plasma

The pooled plasma samples have been stored for a period of more than 2 years at —20°C. The values obtained after 5 days, 1 month 1 year and 2 years are shown in Table VII When the 5 days and 1 month samples were run the laboratory standard was GF 25 26 3 For the remaining samples the laboratory standard was GF 29 2 No difference in obtained HGH values was noted after 2 years storage at —20°

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TABLE VIII *Effect of room temperature on whole blood and plasma*

	HGH n g/ml plasma. Mean ± S D f 5 estimations			
	Neonatal		Adolescent	
Time	blood	plasma	blood	plasma
10 min	20 2 ± 0.7	19.2 ± 1.2	3 6 ± 0 3	4 0 ± 0.5
20 mi	19 5 ± 0 4	19 4 ± 0.9	3 2 ± 0 9	3 6 ± 0.3
60 min	18 3 ± 0 7	20.1 ± 1.3	4 0 ± 0.7	4 3 ± 0.5
2 hrs	17.2 ± 0 4	20 3 ± 1.2	3 2 ± 0.5	4 2 ± 0.4
4 hrs	16 9 ± 0.7	19 6 ± 1 0	7 ± 0 9	4 1 ± 0.6
6 hrs	16 1 ± 0 8	18 8 ± 0.8	0 ± 0 8	3 9 ± 0.5
14 hrs	13.2 ± 0.9	17 1 ± 0.9	1 6 ± 0.9	3 7 ± 0.4
24 hrs	8.5 ± 1 1	15 5 ± 1 0	1 0 ± 0 7	3.2 ± 0.5
48 hrs	5 2 ± 1.0	13.5 ± 1 1	<0.5	2.5 ± 0 6

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Tubes containing 0.8 ml of pooled plasma were thawed and frozen various times. All samples were estimated in the same series. The results are shown in Table IX and show no effect of repeated thawing.

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2	20.5±1.1	3.2±0.8
5	21.8±1.6	3.7±0.3
10	21.7±1.9	3.4±0.7

Effect of hemolysis on plasma levels of immunoreactive growth hormone

Freshly drawn blood samples, one cord blood, one from a healthy 11 year old child were divided into 2 parts, the major portion was spun, the plasma separated and frozen. The minor part was immediately frozen to receive 100 % hemolysis without adding any substances. Twentyfour hours later the samples were thawed and different amounts of the hemolyzed blood were added to the plasma samples. The degree of hemolysis was measured by the method described by Marinek (1966). Results in Table X show that a fairly high amount of hemolysis is tolerated without interfering with the analysis. Very large amounts however will *result in* decreasing levels of HGH as well as an increase in S.D. Several explanations for the decrease of estimated immunoreactive HGH values are possible. One possibility is dilution of plasma with the intracellular fluid since the amount of HGH in the cells certainly is lower than in plasma. Furthermore the hemoglobin might act as a blocking agent on labeled HGH, which would simulate a decrease of available ^{131}I HGH, and with constant amount of antiserum the B/(B+F) ratio would increase, giving a lower HGH value. More probably however the hemoglobin interferes with the buffer flow chromatography. Hemoglobin moves away *from* the application line as do other proteins. Probably it is able to carry away some of the antibody *free intact* ^{131}*I HGH.* This explanation also accounts for the fact that incubation damage as measured in control samples without antibody increases with increasing amount of hemolysis, giving an increase in S.D.

TABLE X. *Effect of hemolysis on HGH levels*

Per cent hemolysis	HGH in ng/ml plasma. Mean ±S.D. of 5 estimations Neonatal plasma	Adolescent plasma	Per cent hemolysis
0.005	75± 5.4	4.3±1.2	0.004
0.3	72± 4.0	3.7±0.9	0.4
0.8	78± 4.8	4.8±0.8	0.8
2.4	72± 5.2	4.0±1.3	2.3
10	68± 6.8	±1.9	9.8
65	56±10.2	1.5±2.0	60
100	32±15.1	<1.0±2.0	100

Evaluation of the method

Recovery of exogenous HGH

The recovery of added HGH to neonatal and adult blood was studied The neonatal blood was drawn from a five day old infant of a diabetic mother the adult blood from a 25 year old student. The blood samples were divided in two equal parts one for recovery in blood, one for recovery in plasma. As for recovery in blood, the samples were rocked in room temperature 15 minutes after the addition of exogenous growth hormone and prior to the separation of the plasma. Plasma and blood samples were allowed to stand at room temperature for about 25 minutes including centrifugation time. The results are shown in Fig 19 and are summarized in Table XI

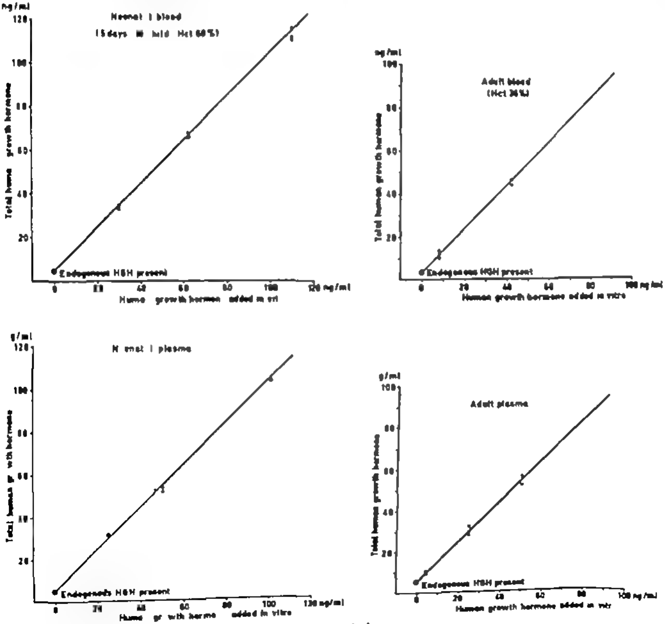
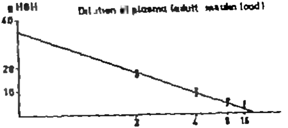


Fig 19 Recovery of exogenous HGH The lines indicate 100 % recovery

TABLE XI *Recovery of exogenous HGH*

Source	Per cent recovery (range)
Neonatal blood	97—107
Neonatal plasma	87—109
Adul blood	84—116
Adult plasma	92—110



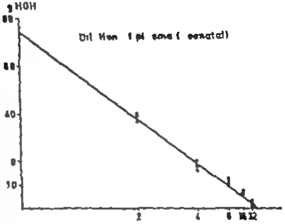


Fig 20 Dilution f plasma. Lines indicate teoretical dilution of simulate f undiluted plasma is true

Reproducibility

The results of the estimation of the two pooled samples (page 23) run on 20 different occasions over a period of 9 months were compared. The mean and S.D of the "between assay estimations were 33.38 ±1.7 ng/ml for the pooled neonatal plasma and 4.26 ±0.76 ng/ml for the adolescent plasma. This study was followed by a within comparison where 20 samples of both pooled plasmas were run in the same series. The within mean and S.D were 33.3 ±1.0 ng/ml and 4.2 ±0.58 ng/ml.

Accuracy of the assay

This has been studied in two ways.

1 Dilution of plasma. Plasma samples from an infant aged 6 hours and from a 25 year old student during insulin load were diluted serially No attempt was made to correct for arious amounts of protein during the incu bation of the samples. However for the buffer flow chromatography the total amount of protein was kept constant by addition of arious amounts of 7 /o bovine serum albu mi in 0 9 / saline. The results are shown in Fig 20 If accuracy is defined as the per cent of true level, the accuracy range is 94—120 /o for the adolescent plasma and 96—121 /o for neonatal plasma. If the results are subjected to a student s t test the variations do not significantly deviate from 100

– The 95 /o confidence limits with deter minations in triplicates were studied for plasma samples with respect to the variations in the standard curve. Such variations are not taken into account if the λ-value (S.D of points around the regression line divided by the slope of the regression line) is estimated which has been used by some authors (Hales and Randle 1963 Ceran et al. 1966) The 95 % confidence limits were about 20 % of the estimate which is in the same range as for other methods for immunoassay

Evaluation of the method

Recovery of exogenous HGH

The recovery of added HGH to neonatal and adult blood was studied. The neonatal blood was drawn from a five day old infant of a diabetic mother the adult blood from a 25 year old student. The blood samples were divided in two equal parts, one for recovery in blood, one for recovery in plasma. As for recovery in blood, the samples were rocked in room temperature 15 minutes after the addition of exogenous growth hormone and prior to the separation of the plasma. Plasma and blood samples were allowed to stand at room temperature for about 25 minutes including centrifugation time. The results are shown in Fig 19 and are summarized in Table XI

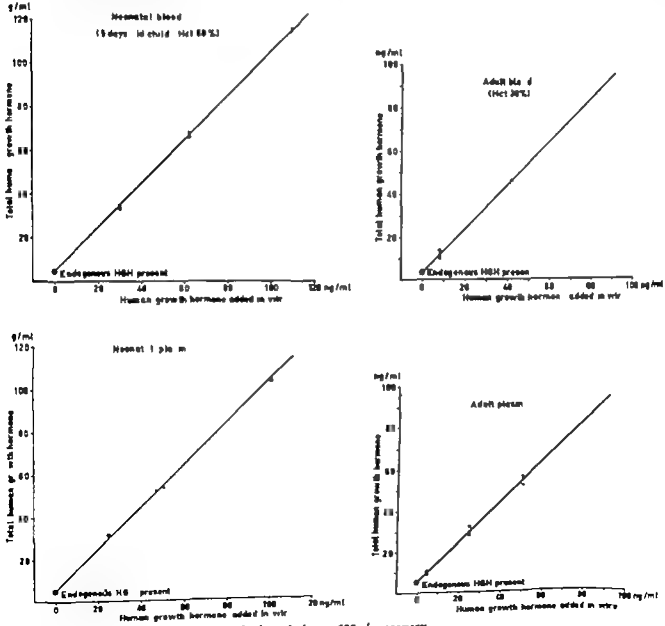


Fig 19 Recovery of exogenous HGH The lines indicat 100 / recovery

Clinical test of the method

The method has been tested on different groups of patients in order to compare the results obtained with those published by others.

Hypophysectomized patients

Two patients with certain total hypophysectomy for craniopharyngioma have been studied on several occasions after the operation. In all of totally 8 different plasma samples the obtained HGH level was <0.2 ng/ml when studied in the most sensitive assay used (page 19).

Acromegalic patients

The results are summarized in Table XII. The results agree with those published by Glick et al. (1963) and Hartog et al. 1964 a). Three acromegalic patients were studied during surgical hypophysectomy and the survival of endogenous HGH was observed. The results for two of the patients are shown in Fig. 21 and ... The half time for HGH for two of the patients was 24 and 28 minutes respectively. For the third patient surgical complications made the hypophysectomy very doubtful and that is proved by the half time of 150 minutes. All patients showed some persistent HGH secretion following hypophysectomy. This is consistent with previous studies (Glick et al 1964). The adherence of the capsule of the eosinophilic adenoma to surrounding blood vessels seems to make a total surgical extirpation impossible.

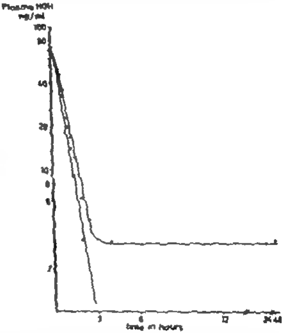


Fig. 21. Disappearance of growth hormone after hypophysectomy on ... acromegalic patient. —— indicate actual levels measured, o—o plasma levels after subtraction of residual constant concentration of 3 ng/ml. T ½ was calculated to be 24 minutes.

TABLE XII. *Fasting levels of HGH in acromegalic patients*

Source	No. of patients	Mean ± S.D. HGH ng/ml	Range HGH ng/ml
Acromegalic low activity	3	23 ± 12.1	12— 36
Acromegalic high activity	3	103 ± 26.3	71—138

Sensitivity

The sensitivity of the assay is expressed as the lowest HGH concentration giving a significant decrease in B/(B+F) ratio. The comparison is made between the B/(B+F) ratio in tubes where no standard HGH was added and the B/(B+F) ratio which corresponds to 0.5, 1 and 2 ng/ml. In 20 consecutive standard curves studied 14 showed differences between 0 and 1 ng/ml. All showed differences between 0 and 2 ng/ml ($p < 0.01$). So the sensitivity of the assay was on the level of 1 ng/ml. If the sensitivity was studied in the more sensitive system (Fig. 14) it was found to be on the level of 0.5 ng in all 10 standard curves studied.

Clinical test of the method

The method has been tested on different groups of patients in order to compare the results obtained with those published by others.

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Two patients with certain total hypophysectomy for craniopharyngioma have been studied on several occasions after the operation. In all of totally 8 different plasma samples the obtained HGH level was <0.2 ng/ml when studied in the most sensitive assay used (page 19)

Acromegalic patients

The results are summarized in Table XII. The results agree with those published by Glick et al. (1963) and Hartog et al. 1964 a) Three acromegalic patients were studied during surgical hypophysectomy and the survival of endogenous HGH was observed. The results for two of the patients are shown in Fig. 21 and 22. The half time for HGH for two of the patients was 24 and 28 minutes respectively. For the third patient surgical complications made the hypophysectomy very doubtful and that is proved by the half time of 150 minutes. All patients showed some persistent HGH secretion following hypophysectomy. This is consistent with previous studies (Glick et al. 1964) The adherence of the capsule of the eosinophilic adenoma to surrounding blood vessels seems to make a total surgical extirpation impossible.

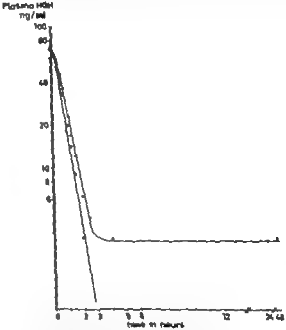

Fig. 21 Disappearance of growth hormone after hypophysectomy in acromegalic patient. —— indicate actual levels measured o—o plasma levels after subtraction of residual constant concentration of 3 ng/ml T½ was calculated to be 24 minutes.

TABLE XII *Fasting levels of HGH in acromegalic patients*

Source	No. of patients	Mean ± S.D. HGH ng/ml	Range HGH ng/ml
Acromegalic low activity	3	23 ± 12.1	1 — 36
Acromegalic high activity	5	105 ± 26.5	72 — 131

Sensitivity

The sensitivity of the assay is expressed as the lowest HGH concentration giving a significant decrease in B/(B+F) ratio The comparison is made between the B/(B+F) ratio in tubes where no standard HGH was added and the B/(B+F) ratio which corresponds to 0.5 1 and 2 ng/ml In 20 consecutive standard curves studied 14 showed differences between 0 and 1 ng/ml All showed differences between 0 and 2 ng/ml ($p < 0.01$) So the sensitivity of the assay was on the level of 1 ng/ml If the sensitivity was studied in *the more sensitive system* (Fig 14) it was found to be on the level of 0.5 ng in all 10 standard curves studied.

Clinical test of the method

The method has been tested on different groups of patients in order to compare the results obtained with those published by others.

Hypophysectomized patients

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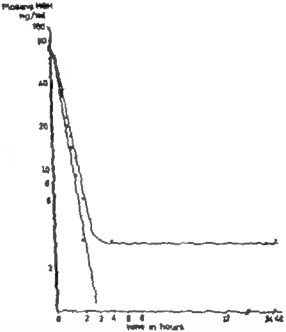

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TABLE XII. *Fasting levels of HGH in acromegalic patients*

Source	No. of patients	Mean ± S.D. HGH ng/ml	Range HGH ng/ml
Acromegalic low activity	3	23 ± 12.1	12— 36
Acromegalic high activity	5	105 ± 26.5	71—138

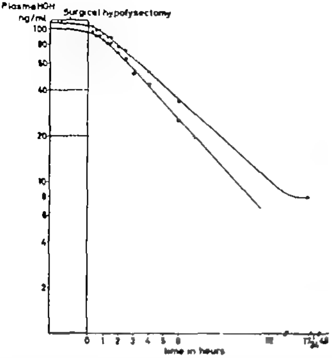


Fig 22. Disappearance of growth hormone after hypophysectomy in a acromegalic patient. — indicates actual measurements o—o plasma levels after subtraction of residual concentration 9 ng/ml. Calculated $T_{1/2}$ is 150 minutes The hypophysectomy was complicated the patient showed clinical signs of acromegaly one month after operation. HGH levels at that time 76 ng/ml.

Cord blood and newborn infants

Samples of cord blood from 10 infants were studied The mean level was 40 2 ±10 6 (S D) This is in agreement with the results published by Cornblath et al (1965) and Laron et al. (1967) A special study of HGH levels in newborn infants is published in Part II

Children and adults

Fasting levels of normal children and adults are very low and not uncommon below 1 ng/ml Only a small series has been studied and the results are summarized in Table XIII They are in agreement with the results of others (Greenwood et al 1964)

It is of much greater interest to study the increase in HGH levels induced by hypoglycaemia first shown by Roth et al. (1963 a) This has been studied in a series of 16 normal children The results are discussed in detail in Part II The HGH response to insulin induced hypoglycaemia has been studied in 10 adults aged 22 to 47 years. The method was identical with that applied to children as described in detail in Part II The amount of insulin used to induce hypoglycaemia was 4 U per square meter body surface.

The results are summarized in Table XIV They are in good agreement with those published in the excellent survey of Greenwood et al. (1966)

TABLE XIII *Fasting levels of HGH in normal children and adults*

Source	No. of patients	Mean ± S.D HGH ng/ml	Range HGH ng/ml
Age 1— 5 years	10	5.2±3 4	<1—12
Age 6—10 years	10	4 4±3 9	<1—11
Ag 11—15 years	10	4 9±3.3	<1—10
Ad lts	10	1.2±1.0	<1—11

TABLE XIV *HGH increase and glucose decrease to insulin-induced hypoglycaemia in adults*

HGH maximal increase. Mean ±S.D	31.2±13.7 g/ml
HGH maximal increase. Range	11 —62 ng/ml
Blood glucose minimal level. Mean ±S.D	29 8± 6.2 mg/100 ml
Blood glucose minimal level Rang	21 —34 mg/100 ml

Use of the labeled ^{131}I HGH for detection of antibodies

The labeled antigen is very useful for the purpose of detecting antibodies. If the labeled antigen when incubated with serum moves from its characteristic position in the free state to the position that in the separating system is occupied by bound antigen, then that serum will contain specific antibodies.

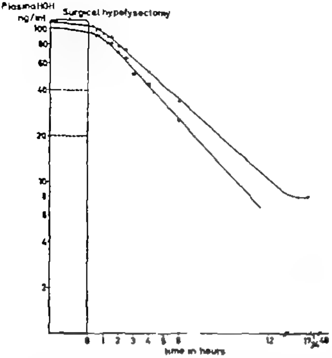
For growth hormone this is of special interest since it has been published that treatment with HGH will give rise to antibodies against HGH in some patients (Szêky et al. 1962 Roth et al. 1964)

Method for detection of HGH antibodies

The serum to be tested was serially diluted 1 1 1 2, 1:4 1 16 1:32, 1:64 etc. with buffer 3 From each dilution step 500 µl was incubated with 0 4 ng ^{131}I HGH for 24 hours at +4 C. The separation was performed with the buffer flow technique. The highest dilution that bound 50 % of the labeled hormone was taken as titre.

Results

All patients treated with HGH in our hands have been repeatedly tested for the presence of antibodies but none have been detected. In two serum samples with earlier proved antibodies (gift from Prof A Prader Zürich, Switzerland) the antibodies have been verified. These two test samples were always run as controls when tests for the presence of antibodies were performed. The only explanation for that is that our patients so far have not produced antibodies. This will be discussed further in Part II.



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Adults	10	1.2±1 0	<1—11

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Method for detection of HGH antibodies

The serum to be tested was serially diluted 1:1 1:2, 1:4 1:16 1:32, 1:64 etc. with buffer 3 From each dilution step 500 µl was incubated with 0.4 ng ^{131}I HGH for 24 hours at +4°C. The separation was performed with the buffer flow technique. The highest dilution that bound 50 % of the labeled hormone was taken as titre.

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CHAPTER VIII

General discussion

In the radioimmunoassay it is assumed that the radioactively labeled and unlabeled hormones behave identically and that the circulating hormone is chemically and immunologically identical with the standard hormone preparation

The growth hormone used for this study has been prepared by the method of Roos et al (1963) The method of preparation is rather mild all procedures being performed in solutions of nearly neutral pH, and the method is favored by many investigators since the product seems less heterogeneous than most other preparations (Donato et al. 1966) This growth hormone however can be separated into several fractions as can other available preparations (Raben 1959 Ferguson and Wallace 1961 Gumbach and Kaplan 1962, Roos et al 1963 and Hunter 1965) In most instances such fractions have been shown to possess identical antigenic and/or biological activity (Gumbach and Kaplan 1962) In some, however quantitative differences have been shown (Ferguson and Wallace 1963 Hunter 1965) For the growth hormone used in this study it has been shown that one of four fractions, a minor portion of the total hormone preparation, has a decreased immunological activity but identical biological activity when compared with the other fractions Furthermore Trygstad (1967) has been able to separate a lipid mobilizing factor from the crude human pituitary extract and the subsequent separation of growth hormone yielded a more homogeneous somatotrophic hormone which gave a somatotrophic activity that was about 25 % higher on a weight basis than the HGH prepared according to the method of Roos et al (1963) That would agree with the suggestion by Levine and Luft (1964) that what we call HGH is a combination of two hormones one a growth promoting and the other a metabolic hormone. Available HGH would probably contain these two hormones in varying proportions.

Since radioimmunoassay is an inhibition technique and since plasma inhibits the reaction between labeled HGH and its antiserum, the plasma contains a protein which is immunologically identical with standard HGH obtained from human pituitaries if there is an exact parallel between equal dilutions of standard HGH and plasma. That is shown for this HGH preparation in Fig 20 and has been shown for other preparations (Hunter and Greenwood 1964) Until the growth hormone from plasma is quantitatively isolated and characterised it cannot be proved if its biological activity is similar to the immunological activity and if the immunological activity measured is representative for the metabolic and/or the somatotrophic action of HGH. Thus the HGH concentration in plasma obtained with radioimmunoassay should be called immunoreactive growth hormone The results published by different investigators however do not differ greatly and so far the method studied above is no exception. In the near future an international standard will be presented by W H.O This will make it easier to compare results obtained in different laboratories.

The preparation of labeled growth hormone and antiserum used for the method described above is similar to those used by other authors. The labeled hormone seems to be comparable with those used in other methods. The antiserum shows a sufficient avidity to the antigen giving a slope of the

standard curve (Fig. 5) of about 8 %. (The slope is defined as the decrease in per cent bound per doubling dose of standard (Hunter 1967 a). The steeper the slope of the standard curve, the greater the discrimination between two unknown samples and the greater the precision.) The slope is sufficient to give good precision but not so steep that the working range is restricted.

The problem of damaged HGH has been neglected in many radioimmunoassay systems. Berson et al. (1964) have stated that the sensitivity and precision of immunoassays is dependent upon the amount of damaged hormone present. For the present method it is shown that an increase in incubation damage will diminish the slope of the standard curve, and that will decrease the precision, with a corresponding increase in S.D. (Table III and Fig. 18).

Damaged HGH as shown by appearance of immunologically inert material may be caused by many factors. 1. Preparation of the hormone. Some studies indicate that HGH preparations prepared from the same starting material but handled in different ways during preparation show varying amounts of damage when labeled simultaneously under the same conditions (Westphal et al. 1968). 2. Manipulation with the hormone. As stated in the study above freezing and lyophylizing of the hormone increased the amount of damage. 3. Iodination of the hormone. a) Alteration of the hormone molecule due to substitution of iodine. If peptide hormones are heavily labeled there seem to be such alterations in the molecule that its immunological and chemical behaviour is altered. For HGH Hunter (1967 a) has shown that such alterations are not detectable if 7 or less atoms of iodine are substituted on the molecule. The labeling procedure used in this study will give less than 1 atom of iodine per molecule of protein. b) Radiation damage. This has been minimized in many ways. All reagents are kept as concentrated as possible, the total amount of ^{131}Iodide (2 mc) is small and the time of preparation very short. The separation on Sephadex is fast and after preparation the ^{131}I HGH is protected by the addition of protein and diluted. c) Chemical damage due to reagents used for labeling. Greenwood et al. (1963) could not prove any damage caused by chloramine-T when used in their labeling technique. Later Glover et al. (1967) stated that some damage of the protein may be due to the use of chloramine-T. The labeling method used in this investigation should be studied to see if a decrease in the amount of chloramine-T and consequently in meta-bisulfite will decrease the amount of damage without greater decrease in the yield of the labeling procedure resulting in decrease of the specific activity. d) Chemical damage due to noxious impurities in the radiochemical reagent. Such must occur at irregular intervals. As stated before, in periods the labeling has given a labeled product with a high amount of damage and a low yield of the labeling procedure. The results were identical for insulin when insulin and HGH were labeled simultaneously in this laboratory. The same experience has been claimed by Yalow and Berson (1967) and Hunter (1967 b). In 1963 Hunter was able to label HGH with specific activities up to 600 μc/μg using 4 mc ^{131}Iodide for 5 μg HGH without detectable damage. Since 1964 however damage frequently has occured when 2 mc were used for 5 μg HGH. It is an urgent desire of all concerned with labeling of proteins with these radioisotopes that the commercial producers of the isotope solve this problem. 4. Incubation with plasma. This problem has been discussed in detail for insulin by Yalow and Berson (1964). Incubation of ^{131}I HGH with diluted plasma (1:5 or more) will give only minor interference but the longer the incubation time the more pronounced is the problem. For this method it is shown in Fig. 16 that the increase of S.D. in the 6 days incubated samples is caused by increasing damage. The damage is caused by the protein and is due to alteration in the

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physio-chemical and immunological properties of the labeled antigen The potency to cause damage seems to vary between different plasmas It is not prevented by the enzyme inhibitor difluorophosphate (Roth et al. 1964)

A factor not previously studied is the influence of hemolysis. As shown in Table X a moderate hemolysis can be tolerated while a pronounced hemolysis increases the incubation damage as it is tested in this system. To the author's knowledge no studies of the influence of hemolysis in other immunoassay systems have been published, so it is not possible to decide whether the effect of hemolysis is general or affects only the buffer flow chromatography separation used in this study

In the immunoassay described above, as well as in systems using electrophoresis or chromato-electrophoresis for separation of free and antibody bound hormones the damaged hormone will move with the antibody bound. If no correction for the damage is performed it will result in an underestimation. Thus for the standard curve as well as for each separate plasma estimated the approximate total amount of damage has been calculated as has been described earlier An upper limit of damage has been stated to be about 35 %.

Of other separating systems, the double-antibody technique is the most frequently used (Utiger & Parker 1962, Hartog et al. 1964 a, Schalch and Parker 1964 Cerasi et al. 1966 and Root et al. 1967) The interference of damage has not been discussed by the authors but should result in an overestimation since the immunologically inert damaged components are held in solution and read as free antigen. Some other factors however will influence the results in the opposite direction. Morgan et al (1964) showed a heat labile plasma inhibitor and that the method was influenced by the total amount of protein. Cerasi et al (1966) demonstrated that different HGH levels could be obtained when the amount of antiserum or the incubation time was changed. So the double antibody system causes several difficulties that make comparison between HGH levels obtained via different separation methods delicate

Storage of blood plasma samples The method used has been carefully tested especially for its application on neonatal plasma. However no differences between adolescent and neonatal plasma with regard to their behaviour in the assay have been proved with one exception When plasma or blood is kept at room temperature the HGH levels obtained successively decrease For adolescent plasma no alteration is noted within 24 hours, a fact which would permit transport of plasma without freezing or other precautions from a wide area surrounding the laboratory For neonatal plasma however a significant decrease can be noted after 14 hours. As for whole blood a significant decrease will be detectable after 4 hours for adolescent blood and within 2 hours for neonatal. The storage at room temperature is not followed by any increase in incubation damage. The reason for the decreased HGH levels measured may be due to changes in the immunological activity induced by enzymes in plasma and blood. Experiments with enzyme inhibitors however have not been performed. Consumption of growth hormone by the corpuscular element of the blood is another possibility However storage of plasma at —20°C will completely inhibit alterations in plasma since estimation of identical plasma over a time interval of two years gave identical results. Neither does freezing and thawing plasma give any changes in HGH levels obtained

CHAPTER IX

Final conclusions

The radioimmuno-chromatographic assay for HGH described seems suitable for the study of immunoreactive growth hormone in neonatal and adult plasma. The precision and sensitivity is comparable with other assays published, and the results obtained agree with those published by others. The problem of degradation damage has to be given special attention. However it is simple to make adequate corrections. The incubation time of four days permits a convenient laboratory routine and the capacity is sufficient for most purposes. The prepared labeled ^{131}I HGH and the flow chromatography separation are suitable for detection of antibody against HGH which is of importance for patients treated with HGH.

physio-chemical and immunological properties of the labeled antigen The potency to cause damage seems to vary between different plasmas. It is not prevented by the enzyme inhibitor difluorophosphate (Roth et al 1964)

A factor not previously studied is the influence of hemolysis. As shown in Table X a moderate hemolysis can be tolerated, while a pronounced hemolysis increases the incubation damage as it is tested in this system. To the author's knowledge no studies of the influence of hemolysis in other immunoassay systems have been published, so it is not possible to decide whether the effect of hemolysis is general or affects only the buffer flow chromatography separation used in this study

In the immunoassay described above, as well as in systems using electrophoresis or chromato-electrophoresis for separation of free and antibody-bound hormones, the damaged hormone will move with the antibody bound. If no correction for the damage is performed it will result in an underestimation Thus for the standard curve as well as for each separate plasma estimated the approximate total amount of damage has been calculated as has been described earlier An upper limit of damage has been stated to be about 35 %

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PART II

Clinical Study of Human Growth Hormone in Children and Newborn Infants

PART II

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CHAPTER X

Introduction

Since the radioimmunoassay for growth hormone became available in 1963 our knowledge of the regulation and function of growth hormone has rapidly increased. The first investigations (Hunter and Greenwood, 1964) showed rather low HGH levels in infants as well as in adults: the differences between patients were fairly large and normal control subjects showed resting levels of less than 1 ng/ml, which was the lowest sensitivity in routine assay for most methods. Roth et al. (1963 b) were the first to show that the HGH level was influenced by the actual blood glucose level. Hypoglycaemia was followed by a marked increase in plasma HGH if induced by insulin or by infusion of fructose or by 2-desoxy D glucose. Hyperglycaemia following glucose administration decreased growth hormone levels, but the subsequent decline of blood sugar concentration was followed by an increase in growth hormone. This made it possible to suggest tests for growth hormone release. A standardization of a test for the hypothalamo-pituitary axis and the secretion of growth hormone has been studied and proposed by Greenwood et al. (1966).

In the present study the HGH levels during the intravenous insulin tolerance test have been studied in four groups of patients.

1. Normal children.
2. Children with retardation of growth.
3. Children during long term treatment with corticosteroids.
4. Normal infants, infants of diabetic mothers and premature infants during the first week of life.

The growth hormone estimations have been performed by the method described in Part I. Thus the HGH levels obtained represent immunoreactive growth hormone.

In addition the results of treatment with HGH prepared by the method of Roos et al. (1963) will be presented.

Growth hormone release during insulin tolerance test in normal children

The first study of growth hormone levels in normal children was published by Hunter and Greenwood (1964). They showed that fasting levels in children were somewhat higher than those in adults but even in normal children fasting plasma samples may contain less than 1 ng/ml of HGH. Several authors (Roth et al. 1963 b Frantz and Rabkin 1964 and Greenwood et al., 1966) have published data about HGH response to insulin induced hypoglycaemia in adults but until recently only small series are published about similar studies in normal children (Greenwood 1964 Root et al. 1967 Parker et al. 1967 and Kaplan et al. 1968). The purpose of the present investigation was to study the HGH release due to insulin-induced hypoglycaemia in normal children.

Material and methods

Subjects. Sixteen children aged 5 to 15 years with normal growth and without any suspicion of endocrine disease were studied. They were all admitted to the hospital and were accustomed to the hospital routine.

Insulin tolerance test. Prior to the study the children fasted at least 12 hours. The test was started at about 8 o clock in the morning. A scalp vein needle was put in a peripheral vein and a slow saline infusion was started and maintained throughout the test to prevent clotting and make an immediate infusion of glucose possible. The total amount of saline infused did not exceed 100 ml. Before a blood sample was drawn the first ml containing blood and saline was discarded.

Crystalline insulin (Vitrum, Stockholm, Sweden) 4 U per square meter body surface was diluted to 1 ml in 0.9 % saline and injected I.V. followed by a wash of about 5 ml physiological saline. The insulin amount used in this study corresponds to about 1.5 U per kg body weight. Blood samples were withdrawn prior to, and 15 30 45 60 75 90 and 120 minutes after the injection of the insulin. The blood was put in glass tubes containing a small amount of heparin (Vitrum, Stockholm, Sweden). Blood for glucose estimation in duplicate was withdrawn immediately and precipitated. The glass tubes were placed in a beaker containing pieces of ice and when all samples were taken, the blood was spun down, the plasma withdrawn and frozen.

Blood glucose determinations were performed by an enzymatic method using 0.025 M NaOH and 10 % $ZnSO_4 - 7H_2O$ as precipitating agents (Hjelm and de Verdier 1963).

Growth hormone was estimated by the method described in Part I. All estimations were made in triplicate. Control samples for the estimation of incubation damage were taken from the first and the last tube of every load and the mean was used for correction of the bound fraction (page 13).

Results

The results are summarized in Table XV.

The blood glucose decrease was sufficient, the lowest levels were less than 50 % of fasting levels. In most of the children a slight sweating 25—30 minutes after the insulin gift was noted and few complained about moderate dizziness but it was not necessary to interrupt the test in any patient.

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In the present study the HGH levels during the intravenous insulin tolerance test have been studied in four groups of patients

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The growth hormone estimations have been performed by the method described in Part I Thus the HGH levels obtained represent immunoreactive growth hormone.

In addition the results of treatment with HGH prepared by the method of Roos et al (1963) will be presented.

TABLE XV *Growth hormone and blood glucose levels during IV insulin tolerance test in 16 normal children aged 5—15 years*

Case	Age Years/Months	Sex	Time in minutes HGH in ng/ml Blood glucose in mg/100 ml 0	15	30	45	60	75	90	120
1	5/1	f	4 56	6 34	41 [illegible]	62 3[illegible]	39 48	17 52	10 60	2 68
2	6/2	m	4.5 72	7 38	38 36	44 44	31 58	20 75	12 6	<1 69
3	7/3	f	1.5 [illegible]	3.5 40	38 30	30 38	4 51	21 [illegible]	10 72	7 78
4	7/6	m	<1 82	7 41	44 38	58 42	24 54	18 70	8 75	<1 72
5	8/4	m	1.5 67	7 40	18 32	44 42	40 57	18 65	16 71	5 67
6	9/4	f	2.5 72	1.5 37	14 30	12 48	10 59	5 69	7 77	3 65
7	9/4	m	5.5 54	5 31	10 23	28 56	32 49	30 55	21 62	5 65
8	10/3	f	3.5 60	5 [illegible]	12 28	21 37	18 51	1 59	8 71	2.5 [illegible]
9	10/7	m	6 73	7 40	25 24	20 38	18 48	15 55	5 75	<1 88
10	11/0	f	<1 68	2 41	10 31	18 42	24 57	16 64	10 73	8 92
11	11/3	m	3 78	6 37	10 30	17 47	13 [illegible]	10 65	8 76	8 63
12	12/1	f	4 55	6 56	12 23	27 38	26 51	19 60	12 71	10 64
13	[illegible]/8	f	5.5 72	8 39	18 31	38 44	29 57	21 62	10 71	12 67
14	13/2	m	2 88	10 51	32 39	43 49	35 57	18 68	<1 79	1.5 92
15	14/9	f	7 63	9 38	17 29	28 41	20 55	14 68	8 71	1 65
16	15/6	m	4 59	5 31	24 24	32 38	29 51	22 59	10 71	8 63

The mean ± S D of the fasting *level of HGH* was 4 1 ± 2.4 ng/ml with a range between <1 (in two patients) to 8 ng/ml The peak level in most patients (10/16) was obtained 45 minutes after the insulin gift. Four patients reached their peak levels 30 minutes after the insulin injection and two after 60 minutes. The mean increment ± S D from the fasting level was 29 1 ± 11 5 ng/ml The *highest increments* occurred in the youngest children. The response fell with increasing age until a minimum was reached at the age of 11 years. Then the response increased again (Fig. 23)

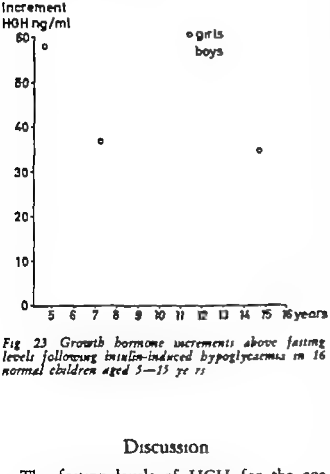

Fig 23 Growth hormone increments above fasting levels following insulin-induced hypoglycaemia in 16 normal children aged 5—15 ye rs

Discussion

The fasting levels of *HGH for the age* group studied corresponds well with those published by Greenwood et al (1964) and are slightly higher than those published by Root et al (1967) and Kaplan et al (1968)

The HGH *response* to hypoglycaemia in children is comparable with the response now *found in* adults (page 30) and in agreement with the results found in children by Greenwood (1964) using an electrophoretic technique. The results of Parker et al. (1967) are comparable with the present results since no differences were shown between children and adults. However their HGH levels are slightly lower than the present results and those of Greenwood et al (1966) This is probably explained by Parker s double antibody technique A lower response in children is reported by Root et al (1967) using a double antibody technique and by Kaplan et al (1968) using a chromato-electrophoretic technique. However no parallel studies of children and adults have been published by any of these authors. Several reasons for this difference between the studies are possible. There are variations in the immunoassay techniques as well as in HGH standards since no international standard is available at this time Another factor not studied in detail is the effect of different amounts of insulin used to induce hypoglycaemia. In the excellent survey of HGH response to insulin induced hypoglycaemia in adults by Greenwood et al. (1966) it was shown that the HGH response varied with the amount of insulin Most reliable results were obtained with an insulin amount of 0 15 U per kg body weight. In the present study the amount of insulin (4 U/m²) corresponds to about 0 15 U per kg body weight. In all other studies on children mentioned above however 0 1 U/kg was used. The suggestion by Kaplan et al. (1968) that *the reason for the depressed response* in HGH to hypoglycaemia in children is due to an altered sensitivity of the hypothalamus could be supported by the present study The greater amount of insulin used in this study induced a more powerful stimulus to the hypothalamus resulting in a pronounced HGH release.

In the present study the HGH response seems to change with the age of the patient. The highest response is obtained in the ranges 5—7 and 13—15 years, periods of most rapid growth. The same age variations have been found by Stimmler and Brown (1967) and

TABLE XV *Growth hormone and blood glucose levels during IV insulin tolerance test in 16 normal children aged 5—15 years*

Case	Age, Years/Months	Sex	Time in minutes HGH in ng/ml Blood glucose in mg/100 ml							
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Growth hormone release during insulin tolerance test on children of short stature

The diagnosis of hypopituitary dwarfism in children has been a matter of great difficulty. Stunted growth is the obligate symptom but since this is a common occurrence in childhood the differential diagnoses have made necessary a number of time demanding investigations which too often have not yielded a precise answer. Previously it was believed that the growth in hypopituitarism in children was not impaired during the first two years of life. However in the review of Brasel et al. (1965) it was stated that in nearly half of the children with idiopathic hypopituitarism the growth was retarded at the age of two years and 35 % showed growth retardation already at the age of one year. This is in agreement with the results of Aarskog (1963). Absence of gross structural abnormalities such as craniopharyngioma and of deficiency in other trophic hormones measurable by functional defects in the target glands, make the diagnosis idiopathic hypopituitarism very difficult. An increased insulin sensitivity has been used to confirm the diagnosis hypopituitary dwarfism and the blood glucose levels during insulin glucose tolerance test (Trygstad 1965) were the main diagnostic evidence for Seip and Trygstad (1966) to find patients suitable for HGH treatment.

Measurement of growth hormone levels in children of short stature became possible in 1963 and studies on patients with stunted growth have been published by Root et al. (1967) Parker et al. (1967) Frohman et al. (1967) Stimmler and Brown (1967) and Kaplan et al. (1968). In the present investigation children with suspected hypopituitarism primordial dwarfism, constitutional growth retardation, Turner's syndrome and chondrodystrophy have been studied. The aim of the investigation was to study the HGH response to insulin-induced hypoglycaemia on children of short stature and to see whether a subnormal response as defined in Chapter XI was correlated to hypopituitary dwarfism.

Material and methods

Subjects: Growth hormone response to insulin-induced hypoglycaemia has been studied in 31 children of short stature. Furthermore a boy of normal height with a craniopharyngioma was studied prior to and following hypophysectomy. The patients have been divided into four groups: 1) hypopituitary dwarfs, 2) premordial dwarfism and constitutional growth delay, 3) Turner's syndrome and 4) chondrodystrophic dwarfs. The classification was based on criteria stated by Wilkins (1965). Furthermore successful treatment with HGH (chapter XIII) was required for the diagnosis of hypopituitarism. However treatment could not be tried in all children of short stature owing to the limited supply of HGH. Patients with subnormal or borderline HGH response to insulin induced hypoglycaemia as defined in chapter XI have been treated for at least six months. Patients with no clinical signs of hypopituitarism and with normal HGH response have not been treated. Using this basis for classification the groups are as follows.

Hypopituitarism: nine children. In five children with idiopathic hypopituitarism, deficiencies in multiple trophic hormones were found, in two only a single growth hormone deficiency has been shown so far.

Kaplan et al. (1968) in their studies on children of short stature.

The range in HGH response is very wide for all studies presented. This makes it difficult to establish the lowest response that can be accepted as normal when the method is used for the comparison between normal subjects and those with various diseases, especially growth retardation. For the present study a growth hormone increase above 10 ng/ml has been adopted as lower limit. This is in agreement with the studies of Greenwood et al. (1966) and Frohman et al. (1967) and comparable with the results of Kaplan et al. (1968). Borderline response occurs in some cases and further provocation tests may be necessary to prove the right diagnosis, as will be discussed later (Chapter XII).

Summary

The growth hormone response to insulin induced hypoglycaemia has been studied in 16 children aged 5 to 15 years. The mean $\pm$ S.D. HGH increase during hypoglycaemia was 29.1 ± 11.5 ng/ml which is of approximately the same size as earlier found in adults. The response varied with age of the children, the response being most pronounced in the age groups where growth is accelerated.

The results are in agreement with those published by Greenwood (1964) and Parker et al. (1967) but not in agreement with those published by Root et al. (1967) and Kaplan et al. (1968). Differences in HGH standard, immunoassay techniques and amount of insulin used to induce hypoglycaemia are probable explanations for the differences. It is concluded from the results of the present study that a normal response to insulin induced hypoglycaemia can be defined as an HGH increase of 10 ng/ml above fasting levels.

Growth hormone release during insulin tolerance test on children of short stature

The diagnosis of hypopituitary dwarfism in children has been a matter of great difficulty. Stunted growth is the obligate symptom but since this is a common occurrence in childhood the differential diagnoses have made necessary a number of time demanding investigations which too often have not yielded a precise answer. Previously it was believed that the growth in hypopituitarism in children was not impaired during the first two years of life. However in the review of Brasel et al. (1965) it was stated that in nearly half of the children with idiopathic hypopituitarism the growth was retarded at the age of two years and 35 % showed growth retardation already at the age of one year. This is in agreement with the results of Aarskog (1963). Absence of gross structural abnormalities such as craniopharyngioma and of deficiency in other trophic hormones measurable by functional defects in the target glands, make the diagnosis idiopathic hypopituitarism very difficult. An increased insulin sensitivity has been used to confirm the diagnosis hypopituitary dwarfism and the blood glucose levels during insulin glucose tolerance test (Trygstad 1965) were the main diagnostic evidence for Seip and Trygstad (1966) to find patients suitable for HGH treatment.

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Hypopituitarism: nine children. In five children with idiopathic hypopituitarism, deficiencies in multiple trophic hormones were found, in two only a single growth hormone deficiency has been shown so far

In two patients the hypopituitarism was due to craniopharyngioma, one of these was of normal height. HGH deficiency and diabetes insipidus, but without any tumour demonstrable by repeated pneumoencephalograms, were present in one child.

Clinical data pertaining to the patients are summarized in Table XVI

Patients with constitutional growth delay and with premordial dwarfism No distinction is made between these groups since each group probably represents a heterogeneous mixture with respect to etiology Four of the fifteen patients showing borderline HGH response to insulin induced hypoglycaemia and with clinical signs that made hypopituitary origin of the growth retardation probable have been treated for six months with HGH without success and are thus included in this group Clinical data pertaining to these patients are summarized in Table XVII

Five children with Turner s syndrome All five children showed clinical stigmata of Turner s syndrome.

Two patients with chondrodystrophy They showed characteristic clinical and radiological stigmata Clinical data in Table XVIII

Insulin tolerance test The test, including measurements of blood glucose and HGH was permormed as described earlier (page 39)

The thyrotrophic function was studied indirectly by measurement of PBI* using a Technicon Auto Analyzer (1964) The normal range in the laboratory is 3 5—7 5 μg/100 ml

ACTH function was studied indirectly by measurement of the output of 17-OH corticosteroids in urine on oral administration of 3 g metyrapone divided in 6 doses during 24 hours.

The gonadotrophic function was studied in 28 patients. The excretion of urinary FSH** was estimated after extraction according to Johnsen (1958) by the method of Steelman and Pohley (1953) modified using 40 U of HCG per animal one injection per day for three days. The standard preparation used was the 2nd IRP for FSH. Levels less than 4 U/24 hours were undetectable. The LH*** excretion in urine has been estimated by the hemagglutination inhibition technique (Wide et al 1961) in a minority of the patients and by the radioimmunosorbent technique (Wide and Porath 1966) in most patients. The standard used was 2nd IRP for LH. Levels less than 4 U/24 hours indicate insignificant levels

*The karyotype***** has been studied in all patients in cultures of leucocytes from peripheral blood.

Measurements of standing height. In all children height measurements were performed in the morning the first three days in the hospital the mean was accepted as the true height.

Height age was calculated from the diagram of Karlberg Iggbom (1959)

Bone age estimations were performed by the method of Eklöf and Ringertz (1967)

Kindly performed at the Department of Clinical Chemistry U ersity Hospital, Uppsala, Sweden, under the supervision of Ass. Prof C. H. de Verdier

Kindly performed by Ass. Prof B. H. Persson, Department of Gynecology and Obstetrics, Uni ersity Hospital Uppsala, Sweden.

***Kindly performed by Ass. Prof L. Wide, Department of Clinical Chemistry University Hospital Uppsala, Sweden.

****Kindly performed by Ass. Prof K. H. Gustafsson, Head of the Cytogenetic Laboratory of the Peadiatric Clinic U iversity Hospital, Uppsala, Sweden.

I want to express my thank for the generous help with these in estigations.

TABLE XVI *Clinical data on children with hypopituitarism*

Case	Sex	Age, Years/Months	Height, cm	Height age, Years/Months	Bone age, Years/Months	Birth weight, g	Gestation time, Weeks
1	m	5/1	96	3/0	2/6	3600	40
2	m	6/7	97	3/2	4/0	3750	44
3	f	8/2	107	4/7	5/0	1850	35
4	m	15/5	117	6/6	8/0	3200	40
5	m	16/1	138	10/2	10/0	—	—
6	f	18/1	128	8/5	11/0	4000	41
7	m	25/2	135	9/10	10/0	3500	40
8**	f	8/11	114	6/0	7/6	4010	40
9***	m	11/0	126	7/11	9/6	3200	40
10***	m	11/3	150	12/6	12/0	3790	40

*Died in neuroblastoma 5 months after investigation and before start of HGH treatment
**Diabetes insipidus started three years prior to the investigation.
***Hypophysectomized for craniopharyngioma.

TABLE XVII. *Clinical data on children with premordial and constitutional dwarfism*

Case	Sex	Age, Years/Months	Height, cm	Height age, Years/Months	Bone age, Years/Months	Birth weight, g	Gestation time, Weeks
11	f	5/0	95	3/0	4/0	2680	42
12	m	5/8	103	4/0	5/0	2730	39
13	f	6/0	100	3/8	3/6	3900	40
14	m	6/7	104	4/5	6/6	3100	40
15	f	7/6	104	4/5	7/0	2400	38
16	m	8/9	115	6/0	8/6	3050	40
17	m	9/0	102	3/11	4/0	2050	40
18**	m	10/4	100	3/8	8/6	1750	40
19	f	13/2	135	9/9	12/0	2700	39
20	f	13/4	111	5/4	11/0	3380	40
21	m	13/6	139	9/9	13/6	3150	40
22	m	13/7	135	9/9	10/0	3770	40
23	m	13/7	133	9/6	11/0	3160	40
24	m	15/2	124	7/10	13/0	2000	36
25	m	18/0	146	11/8	13/0	3200	40

*Bird headed dwarf
**Male Turner

TABLE XVIII *Clinical data on children with Turner's syndrome and chondrodystrophic dwarfism*

Case	Sex	Age, Years/Months	Height, cm	Height age, Years/Months	Bone age, Years/Months	Birth weight, g	Gestation time, Weeks
26	f	5/0	97	3/2	4/0	2550	40
27	f	11/0	120	7/7	10/6	3420	42
28	f	13/1	135	9/9	13/0	3380	40
29	f	17/1	135	9/9	13/0	2800	40
30	f	21/8	144	11/4	15/0	2800	41
31	m	4/0	94	2/8	4/0	3250	40
32	m	10/1	118	6/9	10/0	3530	40

Results

The increments of HGH to insulin induced hypoglycaemia are compared with the increments for normal children in Fig 24

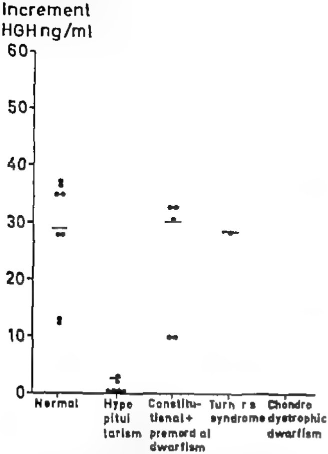

Fig 24 Growth hormone increments from fasting levels following insulin-ind ced hypoglycaemia in 16 n rm l children and 31 children with stunted growth The hori ont l lin s indic t the mean increment for the group

Hypopituitarism Blood glucose and HGH levels are shown in Table XIX. Five of the patients showed a pathological insulin load with low blood glucose levels and persistent hypoglycaemia. In one case (no 2) the insulin load had to be interrupted by glucose infusion 28 minutes after the insulin gift. Two patients had a history of spontaneous hypoglycaemia.

Base levels of HGH were less than 1 ng/ml in six of the patients. Four patients showed no measurable increase in HGH levels during the insulin load and four patients showed subnormal response. Furthermore one patient with stunted growth due to craniopharyngioma showed a subnormal increase and one patient with normal growth in spite of craniopharyngioma showed normal HGH response prior to the operation but failed to increase in HGH after the hypophysectomy

The results of other laboratory investigations are summarized in Table XX.

PBI was decreased and the response to metyrapone was poor in 5 of the 7 patients with idiopathic hypopituitarism. The patients with craniopharyngioma had normal response. Only one patient (one with craniopharyngioma) showed any gonadotrophic activity All patients had a normal karyotype. Height age and bone age were markedly retarded in all patients with HGH deficiency at the time of the study In three of the patients it was possible to detect growth retardation at the age of two years. As the years passed the gap between the child s growth and normal growth increased for all patients.

Constitutional and premordial dwarfism The laboratory investigations are summarized in Table XXI The blood glucose was decreased to less than 50 % of the fasting level in all children with a mean of 41 % of fasting level and a range of 28—47 %. Two patients showed an increased insulin sensitivity with prolonged hypoglycaemia.

Fasting levels of HGH varied between 1 and 8 ng/ml and the maximal increment between 7 and 62 ng/ml with a mean ± S D of 30 9 ± 15 9 ng/ml. This is in agreement with the results obtained with normal children. Two patients showed insufficient HGH increase, defined earlier as an increment less than 10 ng/ml (page 42) and these two patients also showed an increased insulin sensitivity One of them (case 22) had a history of hypoglycaemic weakness. Two patients showed borderline HGH response.

PBI was normal in all children. A poor response to metyrapone was noticed in three patients of which two were the patients with subnormal HGH response and one showed a borderline HGH response. The gonadotro-

TABLE XIX. *Growth hormone and blood glucose levels during IV insulin tolerance test in children with hypopituitarism*

Time in minutes
HGH in ng/ml
Blood glucose in mg/100 ml

Case	0	15	30	45	60	75	90	120
1	2.0 67	2.5 35	4.0 28	5.0 21	3.0 35	<1 40	<1 42	1.5 40
2	<1 69	<1 26	<1 11	<1 310*				
3	1.5 79	1.0 55	2.0 25	2.5 28	3.5 3	3.0 45	3.5 50	<1 55**
4	<1 55	<1 3	<1 18	<1 25	<1 38	<1 44	<1 40	<1 75
5	<1 78	<1 34	3.0 28	5.5 32	4.0 33	3.5 44	<1 48	<1 52
6	<1 58	<1 28	<1 23	<1 22	<1 28	<1 32	<1 37	<1 41
7	<1 68	<1 22	<1 30	<1 20	<1 35	<1 39	<1 47	<1 58
8	1.3 78	1.3 34	4.0 28	5.5 32	5.0 48	4.0 69	1.5 77	2.0 [illegible]
9	<1 70	1.5 32	4.0 32	4.0 57	6.0 65	9.0 63	8.5 64	6.0 70
10	5.5 68	6.5 32	18 30	34 42	28 38	21 72	8.0 78	4.0 75
10 b	<1 77	<1 28	<1 30	<1 38	<1 31	<1 72	<1 82	<1 78

10 prior to operation of craniopharyngioma.
10 b 3 months after operation
After the injection of glucose.
**5 hours after insulin injection the blood glucose was 36 mg/100 ml in spite of two meals in the meantime

phins were moderately elevated in 5 of 7 patients aged 11 years or more. Of the two patients without gonadotrophic activity one showed a subnormal HGH response, and the other a borderline response.

The karyotype was normal in all children. Height age was retarded with a minimum of two years. Bone age was retarded in ten of the patients.

In all patients with Turner's syndrome (laboratory results in Table XXII) the blood glucose fell to less than 50 % of fasting level (mean 40 %, range 31—45 %)

Fasting levels of HGH varied between 3 and 8 ng/ml and the response to hypoglycaemia was of the same order as that for normal children. The mean ± S.D was 28.4 ± 5.7 ng/ml and the range 22—37 ng/ml.

The PBI and the response to metyrapone was normal. The gonadotrophins were high in patients aged 13 years or more. In four patients the karyotype was 44 + XO and in

Results

The increments of HGH to insulin induced hypoglycaemia are compared with the increments for normal children in Fig 24

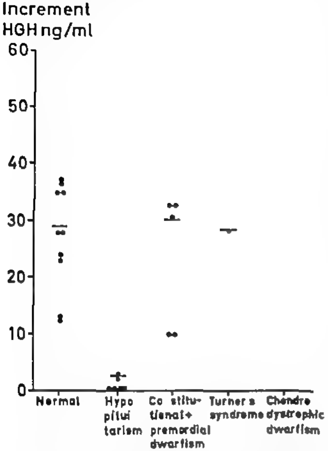

Fig 24 Growth hormone increments from fasting levels following insulin-induced hypoglycaemia in 16 normal children and 31 children with stunted growth The horizontal lines indicate the mean increment for the group

Hypopituitarism Blood glucose and HGH levels are shown in Table XIX. Five of the patients showed a pathological insulin load with low blood glucose levels and persistent hypoglycaemia. In one case (no 2) the insulin load had to be interrupted by glucose infusion 28 minutes after the insulin gift. Two patients had a history of spontaneous hypoglycaemia

Base levels of HGH were less than 1 ng/ml in six of the patients. Four patients showed no measurable increase in HGH levels during the insulin load, and four patients showed subnormal response. Furthermore one patient with stunted growth due to craniopharyngioma showed a subnormal increase and one patient with normal growth in spite of craniopharyngioma showed normal HGH response prior to the operation but failed to increase in HGH after the hypophysectomy

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Fasting levels of HGH varied between 1 and 8 ng/ml and the maximal increment between 7 and 62 ng/ml with a mean ± S D of 30 9 ± 15 9 ng/ml. This is in agreement with the results obtained with normal children. Two patients showed insufficient HGH increase defined earlier as an increment less than 10 ng/ml (page 42) and these two patients also showed an increased insulin sensitivity One of them (case 22) had a history of hypoglycaemic weakness. Two patients showed borderline HGH response

PBI was normal in all children. A poor response to metyrapone was noticed in three patients of which two were the patients with subnormal HGH response and one showed a borderline HGH response. The gonadotro-

TABLE XX. *Laboratory investigations on children with hypopituitarism*

Case	PBI, μg/100 ml	Metyrapone response	Gonadotrophins, Units/24 hours FSH	LH
1	8.1	normal	—	—
2	2.0	poor	—	—
3	3.6	poor	<4	<4
4	2.7	poor	<4	<4
5	4.7	normal	<4	<4
6	3.0	poor	<4	<2
7	3.2	poor	<4	<4
8	5.4	normal	<4	<2
9	4.3	normal	<4	<4
10	[illegible]	normal	<4	6

TABLE XXI. *Laboratory investigations including HGH increments from fasting levels following IV insulin tolerance test in children with premordial and constitutional dwarfism*

Case	PBI, μg/100 ml	Metyrapone response	Gonadotrophins, Units/24 hours FSH	LH	Insulin load	HGH ng/ml, Fasting level	Increment
11	7.2	normal	<4	<4	normal	8	34
12	7.0	normal	<4	<4	normal	3	33
13	8.2	normal	<4	<2	normal	2.5	12
14	6.9	normal	<4	<4	normal	2	28
15	7.3	normal	<4	<2	normal	7	35
16	6.0	normal	<4	<4	normal		33
17	7.8	normal	<4	<4	normal	<1	10
18	5.7	normal	<4	<4	normal	6	38
19	6.2	normal	4	8	normal	2	32
20	5.8	normal	4	8	normal	<1	24
21	5.5	normal	6	11	normal	5	31
22	5.7	poor	<4	<4	pathological	2	9
23	6.7	poor	<4	<4	normal	<1	10
24	4.4	normal	6	8	normal	6	62
25	4.3	poor	6	8	pathological	1.5	7

TABLE XXII. *Laboratory investigations including HGH increments from fasting levels following IV insulin tolerance test in children with Turner's syndrome and chondrodystrophic dwarfism*

Case	PBI, μg/100 ml	Metyrapone response	Gonadotrophins, Units/24 hours FSH	LH	Insulin load	HGH ng/ml, Fasting level	Increment
26	7.3	normal	<4	<4	normal	3.0	37
27	6.3	normal	4	4	normal	6.0	25
28	7.2	normal	100	117	normal	6.0	28
29	5.0	normal	50	40	normal	7.0	22
30	5.2	normal	80	107	normal	8.0	30
31	—	—	—	—	—	3.0	42
32	—	—	—	—	—	6.0	29

one patient the karyotype was 44 + XXL with iso-chromosome for the long arm of the X chromosome The bone age was moderately delayed in the patients aged 17 and 21 years.

The two patients with chondodystrophic dwarfism (laboratory results in Table XXII) showed a normal blood glucose decrease The fasting levels of HGH were 3 and 6 ng/ml respectively and the increments 42 and 29 ng/ml respectively The karyotype was normal as was the bone age.

Discussion

Hypopituitarism Five of the patients showed an *increased sensitivity to insulin* These five children had a poor response to metyrapone so a combination of HGH and ACTH deficiency seems to increase the risks for serious hypoglycaemia. This is in agreement with the results of Kaplan et al. (1968) The blood glucose has not been studied in the period between 20 and 30 minutes after insulin injection which makes a comparison with the study of Trygstad (1965) impossible.

All patients showed low HGH response. This is in agreement with all earlier studies. Five patients with idiopathic hypopituitarism showed a deficiency in corticotrophic as well as in thyrotrophic action

The retardation of bone age was most pronounced in this group of patients when compared to other groups of stunted growth as stated earlier by Clayton et al. (1967)

Constitutional retarded growth and premordial dwarfism The reason for the increased insulin sensitivity in two cases (nos. 22 and 25) combined with spontaneous hypoglycaemia in one of them is not clearly understood Both of them showed a subnormal HGH response, a poor response to metyrapone and a marked retardation of both bone age and height age This made the diagnosis hypopituitary dwarfism probable and the patients were treated for six months with 2 mg HGH twice a week During this period however no increase in growth occurred Two other patients showed border line response to HGH (cases 17 and 23) one of them showing a poor metyrapone response (23) and both having markedly retarded bone age and height age. Even in these patients treatment with HGH had been tried without any acceleration in growth The discovery of patients with stunted growth of non pituitary origin but poor response to insulin induced hypoglycaemia is in agreement with the results of Kaplan et al. (1965) Parker et al (1967) Stimmler and Brown (1967) and Kaplan et al. (1968)

PBI was normal in all patients and the response to metyrapone was normal in all except those discussed above. Gonadotrophins were present in all except two patients aged 13 years or more. Absence of gonadotrophins was noted in cases number 22 and 23 which increased the suspicion of pituitary origin of growth retardation in these patients. To the author's knowledge no studies of gonadotrophins in these groups of patients have been published.

The retardation of bone age varies from patient to patient since the group is rather heterogeneous However the bone age is more retarded in those patients which may be classified as premordial dwarfs. The growth for the constitutional dwarfs seemed to follow normal growth the gap between actual height and normal height was almost constant during the years the patients have been followed. As for most of the premordial dwarfs the gap between actual height and normal height seemed to increase but not to the same extent as in hypopituitarism. This was also found by Clayton et al. (1967)

Turner's syndrome and chondrodystrophic dwarfism The results for the patients with Turner's syndrome are in agreement with the results of Root et el. (1967) and Kaplan et al. (1968) As for the two patients with chondrodystrophy the growth hormone fasting levels and the release was normal. This is in agreement with results found by Beck (1965)

The insulin susceptibility has long been used as a diagnostic test. However in this study as well as in others the insulin sensitivity seems to be marked only in patients where an ACTH deficiency is also present. Furthermore insulin sensitivity may be present without any hyposomatotrophinism.

The tests of other pituitary trophic hormones are valuable in some cases but they are all time demanding and do not prove HGH deficiency.

At this time no method for the study of HGH deficiency seems to be absolute reliable. There are patients on whom available diagnostic tests fail. In such cases a test period with HGH treatment seems to be the only possible way to make a clear diagnosis. It is necessary that this treatment is long enough since short treatment may be misleading due to seasonal changes in growth or due to transient acceleration of growth.

Summary

The HGH response to insulin induced hypoglycaemia has been studied in 31 children with short stature. Ten patients have been classified as hypopituitary dwarfs, and all these patients showed an HGH increment of less than 10 ng/ml from fasting levels. In six of these there were signs of deficiency of other pituitary hormones and two had a craniopharyngioma. In fifteen children the diagnosis was premordial dwarfism or constitutional delay in growth. Two patients in this group showed a subnormal HGH response to insulin-induced hypoglycaemia. In five patients with Turner's syndrome and in two patients with chondrodystrophy the HGH response was normal when compared to a control group. Other parameters compared were the blood glucose levels during the insulin-induced hypoglycaemia, PBI, excretion of 17-OH corticosteroids after metyrapone, urinary gonadotrophins and the bone age. The difficulties in the interpretation of different tests are discussed and some other possible tests for the study of HGH release have been described. On the basis of this study measurements of HGH levels during insulin-induced hypoglycaemia is a useful aid in the diagnosis of hypopituitarism. When borderline results are found further tests or short term therapy with HGH is necessary.

The response to insulin induced hypoglycaemia was less than normal in all patients with dwarfism of pituitary origin However subnormal response was also shown in two patients where HGH deficiency was not the reason for the growth retardation. One factor that influences the HGH response seems to be fasting HGH concentration Frohman et al (1967) and Kaplan et al (1968) have shown that subnormal response to hypoglycaemia is more common in patients where the fasting levels are high. This is not seen in the present study but its absence is probably coincidental and the two patients with subnormal response in this study had low fasting levels of HGH. Hypothyroidism was found to decrease HGH response in three patients studied by Root et al (1967) As shown by Hartog et al (1964 b) and in a study by the author (chapter XIV) glucocorticoid excess also depresses HGH response However there were no signs of hypothyreosis or increased corticosteroid secretion in the two patients with subnormal response

The response in HGH release to insulin induced hypoglycaemia is a very useful test in the diagnosis of hyposomatotrophinism in most cases. The risk of severe hypoglycaemia can be neglected if adequate safeguards including the immediate availability of glucose for intravenous injection are arranged. In most cases the test will yield the correct diagnosis, but since borderline response occurs a number of further tests have been suggested.

The infusion of arginine causes a release of HGH as shown by Knopf et al. (1965) Comparative studies between the HGH release to insulin induced hypoglycaemia and to arginine infusion have been published by Parker et al (1967) and Frohman et al. (1967) The conclusion in both studies is that the arginine provocative test is a complement in the diagnosis of hyposomatotrophinism but even this test is not able to make an exact distinction in every single case. The advantage with the test is that there is no risk for hypoglycaemia.

The effect of vasopressin on HGH levels was studied by Gagliardino et al. (1967) In 15 normal subjects aged four months to 88 years an increase in HGH was measurable 30 to 60 minutes after an intramuscular injection of vasopressin In four hypopituitary patients there was no difference between HGH release to insulin or vasopressin The advantage of this test would be a single provocative test for HGH ACTH (Gwinup 1965) and FSH (Dreyfus et al 1963) However at this time the knowledge about the vasopressin test for HGH release is too small to make it useful as a routine test.

Hyperglycaemia was early shown to induce a decrease in HGH levels, followed by an increase in consequence of blood sugar decrease (Roth 1963 b) This has been studied in detail by Hunter et al (1967) who have described a simple screening test for growth hormone deficiency The increased HGH levels are studied in 2—3 blood samples taken $2^1/_2$ to 4 hours after an oral glucose load of 1 4 g per kg In patients with probable hypopituitarism they found agreement between this test and HGH response to insulin induced hypoglycaemia. The advantage of a glucose test is that it is less unpleasant for the patient and that it probably is a more physiological stimulus.

The metabolic HGH test has been used by some investigators. Prader et al (1964) showed that daily injections of 2 mg/m² of HGH increased the nitrogen retention during the 2nd and 6th day of treatment to a much greater extent in cases of pituitary dwarfism than in cases involving other causes of growth retardation Hubble (1966) showed that the withdrawal of HGH after a test period of 5—9 days induced an increase in nitrogen excretion in non hypopituitary dwarfs while hypopituitary children still retained nitrogen. These metabolic tests, however are very time demanding and require very good cooperation of the patients since nothing seems to be more difficult in practice than an accurate collection of urine.

The four patients with doubtful hypopituitarism (Cases 17 22, 23 and 25 Tables XVII and XXI) did not increase their growth velocity during the treatment. It was continued for at least 6 months since seasonal variations and transient growth accelerations may influence the results if shorter periods are studied.

Antibodies to HGH were not detectable in any patient. Six patients have had treatment for more than 1 1/2 years and two for almost four years.

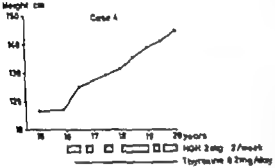

Fig 25 Growth during four years of treatment with HGH

Discussion

The treatment with HGH Roos has accelerated the growth in all patients with hypopituitarism. During the first year of treatment the growth velocity was above normal for age except for one case (no. 10) who was of normal height when the treatment began. During prolonged treatment the growth velocity decreased to a level comparable to normal growth. This should not be considered as a failure of treatment since similar growth response is seen after thyroid treatment for hypothyroidism (Talbot and Sobel 1948). The height increment during treatment in this study is of the same order as reported by others (Aarskog 1963 Raben 1964 Seip and Trygstad 1966, Tanner and Whitehouse 1967 and Prader et al. 1967) The dose of HGH used for treatment in the present study is less than the dose used in most other studies but comparable with that in the study of Rosenbloom (1966) where weekly injections of 2.5 to 5 mg were found to be effective in most patients. The immunoreactive activity of HGH Roos is slightly higher when compared to that of other preparations used for treatment and the same may be true of the biological activity as well. The absence of growth improvement in the four children of doubtful pituitary deficiency is in agreement with earlier attempts to treat other types of dwarfism. It is taken as an indication that the reason for stunted growth in these four patients is not pituitary deficiency

The most encouraging observation in the present study is the absence of antibodies to HGH.

Using HGH Raben (1959) Prader et al. (1967) reported the development of antibodies and the attendant failure to growth in eight of eighteen patients. Tanner and Whitehouse (1967) also found antibodies to HGH Raben in four of nineteen patients. Most patients developed antibodies within a year of treatment, one patient after about $1^1/_2$ years of treatment. The patient studied by Franer and Smith (1966) developed antibodies to HGH Li and Papkoff (1956) within nine months of treatment and Parker et al. (1966) reported development of antibodies to HGH Wilhelmi (1961) in one of thirteen children after seven months of treatment. The risk for development of antibodies after the first year of treatment seems to be negligible. In all studies above the patients who developed antibodies became resistant to further treatment with HGH. However Roth et al. (1964) were able to demonstrate antibodies in three of four patients with long term treatment with HGH but there was no obvious resistance to HGH therapy Kaplan et al. (1968) demonstrated HGH antibodies of low binding capacity in one-third of the patients treated for more than six months. The antibodies apparently did not affect the growth rate during treatment. A possible explanation to these differences in the effect of HGH

Treatment of pituitary dwarfism with human growth hormone

*in collaboration with Paul Roos**

The first successful treatment of a hypopituitary dwarf with human growth hormone (HGH) was reported by Raben (1958). During the following years several authors (Shepard et al. 1960, Vest et al. 1960, Escamilla et al. 1961, Aarskog 1963, Trafford et al. 1963, Soyka et al. 1964, Rosenbloom 1966, Seip and Trygstad 1966, Tanner and Whitehouse 1967, Prader et al. 1967 and Kaplan et al. 1968) have published their results on HGH therapy using various preparations. The general experience of HGH treatment, however, is limited due to lack of sufficient amounts of the hormone.

Only hypopituitary dwarfs have been proved to enhance their growth to HGH. No side effects to treatment with HGH have been reported but a limitation in the treatment is the development of antibodies to HGH. This was first shown for the Raben preparation by Széky et al. (1962). In the present investigation growth acceleration to therapy with HGH according to Roos et al. (1963) has been studied. Tests for the presence of antibodies have been performed in all patients with HGH therapy of 6 months or more.

Material and methods

Subjects. Nine patients with hypopituitary dwarfism (clinical data in Tables XVI and XX, pages 45 and 49) have been treated. Furthermore four patients with doubtful hypopituitarism (cases number 17, 22, 23, 25 in Tables XVII and XXI, pages 45 and 49) have been treated for 6 months. The clinical evaluation of the diagnosis has been described in Chapter XII.

Human growth hormone was prepared by Roos according to the method of Roos et al. (1963). The preparation was stored lyophylised and was dissolved prior to the intramuscular injection in 1 ml 0.9 % saline. The dose was for all patients 2 mg twice a week. Lack of hormone made interruptions in the treatment necessary.

Height was measured every third month during treatment and, if possible, at the same time of the day on all occasions.

HGH antibodies were determined according to the method described in Part I (Chapter VII). Blood samples were taken every six months even if an occasional interruption in the treatment had occurred. All patients were tested for the presence of antibodies in January 1968.

Results

Hypopituitarism. The results are summarized in Table XXIII and shown for case 4 in Fig. 25. The numbering of the patients refers to Tables XVI and XVII. If treatment had been continuous for all patients the height increment during the first year varied between 60 and 160 mm with a mean of 105 mm. For the second year the variation was 75—120 mm with a mean of 92 mm. Mean height increment for the following two years was for the two patients studied about 60 mm per year. No side effects to the treatment were found.

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* Ass. Professor at the Institute of Biochemistry, University of Uppsala. *The preparation of HGH used for treatment has been supported by the Swedish Medical Research Council.*

The four patients with doubtful hypopituitarism (Cases 17, 22, 23 and 25 Tables XVII and XXI) did not increase their growth velocity during the treatment. It was continued for at least 6 months since seasonal variations and transient growth accelerations may influence the results if shorter periods are studied.

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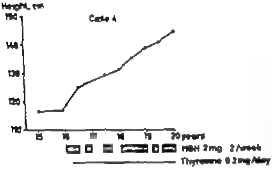

Fig. 25 *Growth during four years of treatment with HGH*

Discussion

The treatment with HGH Roos has accelerated the growth in all patients with hypopituitarism. During the first year of treatment the growth velocity was above normal for age except for one case (no. 10) who was of normal height when the treatment began. During prolonged treatment the growth velocity decreased to a level comparable to normal growth. This should not be considered as a failure of treatment since similar growth response is seen after thyroid treatment for hypothyroidism (Talbot and Sobel 1948). The height increment during treatment in this study is of the same order as reported by others (Aarskog 1963, Raben 1964, Seip and Trygstad 1966, Tanner and Whitehouse 1967 and Prader et al. 1967). The dose of HGH used for treatment in the present study is less than the dose used in most other studies but comparable with that in the study of Rosenbloom (1966) where weekly injections of 2.5 to 5 mg were found to be effective in most patients. The immunoreactive activity of HGH Roos is slightly higher when compared to that of other preparations used for treatment and the same may be true of the biological activity as well. The absence of growth improvement in the four children of doubtful pituitary deficiency is in agreement with earlier attempts to treat other types of dwarfism. It is taken as an indication that the reason for stunted growth in these four patients is not pituitary deficiency.

The most encouraging observation in the present study is the absence of antibodies to HGH.

Using HGH Raben (1959), Prader et al. (1967) reported the development of antibodies and the attendant failure to growth in eight of eighteen patients. Tanner and Whitehouse (1967) also found antibodies to HGH Raben in four of nineteen patients. Most patients developed antibodies within a year of treatment, one patient after about 1½ years of treatment. The patient studied by Fraser and Smith (1966) developed antibodies to HGH Li and Papkoff (1956) within nine months of treatment and Parker et al. (1966) reported development of antibodies to HGH Wilhelmi (1961) in one of thirteen children after seven months of treatment. The risk for development of antibodies after the first year of treatment seems to be negligible. In all studies above the patients who developed antibodies became resistant to further treatment with HGH. However Roth et al. (1964) were able to demonstrate antibodies in three of four patients with long term treatment with HGH but there was no obvious resistance to HGH therapy. Kaplan et al. (1968) demonstrated HGH antibodies of low binding capacity in one-third of the patients treated for more than six months. The antibodies apparently did not affect the growth rate during treatment. A possible explanation to these differences in the effect of HGH

antibodies could be differences in the antibody titre. A comparison can be made with insulin since most patients develop antibodies to insulin with low binding capacity and without interference of response to treatment.

The absence of antibodies in the present study is in agreement with the results of Seip and Trygstad (1966). They were not able to detect antibodies to HGH Roos in two patients after treatment for $3^1/_2$ years. The presence of antibodies was not tested in the other ten patients treated, but none developed resistance to the HGH treatment.

The reason for the finding that HGH Roos probably does not provoke the development of antibodies is not clear. No available HGH preparation is homogeneous, which has been discussed in Part I for HGH Roos. However the preparation procedure of Roos et al. is very mild, the pituitaries are initially frozen and then the material is handled only in aqueous solutions at near neutral pH and all steps are performed at 0—4°C. The extraction in glacial acetic acid and the heating to 70°C in the Raben prodedure may partly denature the hormone. Such a conformational change would be a likely explanation to the observed antigenicity.

Summary

Two mg HGH has been given twice a week to nine patients with pituitary dwarfism and to four children in whom pituitary dwarfism was suspected. All nine patients with proved hypopituitarism increased their growth velocity, the mean height increment during the first year of treatment being 10.5 cm. During the following years the growth velocity approached normal growth. None of the patients became resistant to the treatment and regular tests for antibodies were negative. None of four patients with doubtful hypopituitarism responded to the treatment.

TABLE XXIII *Results of treatment with human growth hormone*

Case	Sex	Age at start of treatment, Years/Months	Growth velocity mm/year before HGH	Growth rate mm/Months of treatment 1st year	2nd year	3rd year	4th year	Additional therapy	Development of antibodies
[illegible]	m	4/11	40	85/12				Thyroxine	ND
3	f	8/2	47	110/12	60/9			Thyroxine	ND
4	m	15/3	18	100/9	80/8	75/12	60/9	Thyroxine	ND
5	m	16/1	11	80/12	60/10			—	ND
6	f	18/1	8	105/12	75/12	40/12	45/12	Thyroxine	ND
7	m	25/2	<5	115/12	60/8			Thyroxine	ND
8	f	8/11	10	90/8				Vasopressin	ND
9	m	11/0	8	40/3				**	—
10	m	11/3	<5*	30/9	30/8			**	ND
17	m	9/0	40	22/6					ND
22	m	13/7	40	15/6					ND
23	m	13/7	44	27/6					ND
[illegible]	m	18/0	22	12/7					ND

ND not detectable.
*Growth during six months between hypophysectomy and start of HGH treatment.
**Operated for craniopharyngioma. Additional therapy Vasopressin, Cortisone and Thyroxine.

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The absence of antibodies in the present study is in agreement with the results of Seip and Trygstad (1966) They were not able to detect antibodies to HGH Roos in two patients after treatment for 3½ years. The presence of antibodies was not tested in the other ten patients treated but none developed resistance to the HGH treatment.

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3	f	8/2	47	110/12	60/8			Thyroxine	ND
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5	m	16/1	11	80/12	60/10			—	ND
6	f	18/1	8	105/12	75/12	40/12	45/12	Thyroxine	ND
7	m	25/2	<5	115/12	60/8			Thyroxine	ND
8	f	8/11	10	90/8				Vasopressin	ND
9	m	11/0	8	40/3				**	—
10	m	11/3	<5*	30/9	50/8			**	ND
17	m	9/0	40	22/6					ND
22	m	13/7	40	15/6					ND
23	m	13/7	44	27/6					ND
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ND not detectable.
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Growth hormone levels in children during long-term treatment with corticosteroids

The administration of corticosteroids has long been known to interfere with normal growth (Blodgett et al 1956) However little is known about the mechanism of the growth inhibition Since the radioimmunoassay for growth hormone made it possible to study the hormone levels in various conditions some studies of the levels during corticosteroid treatment in adults have been published. Hartog et al (1964 b) studied seven patients with corticosteroid treatment and three patients with Cushing s syndrome. They were not able to show any differences in fasting levels of growth hormone. The increase in growth hormone after insulin induced hypoglycaemia, however was diminished for both groups of patients when compared to normal subjects. Frantz and Rabkin (1964) were able to show the same for 11 adult patients treated with long term steroid therapy in various doses Furthermore they demonstrated that the increase in growth hormone levels was less in patients receiving more than 60 mg of Cortisone or equivalent a day Treatment for two days in a dosage of 300 mg Cortisone a day gave a moderate inhibition in growth hormone response. As for children only a small series of five patients currently under long term corticosteroid treatment has been published (Root et al.

TABLE XXIV *Clinical data on 17 children with long term treatment with corticosteroids*

					Treatment with Cortisone eq alents			
Case	Sex	Age Years/Months	Delay in bone age Years/Months	Height increment per centile previous yea	Duration, Years/Months	Total dose gram	Mean dosage mg/day previous year	Mean dosage mg/day previous month
1	f	6/3	—3	<3	3/8	31.3	19 0	19.0
2	m	7/1	—1/3	<3	2/0	12.2	28 1	28.1
3	m	9/0	0	25	5/6	19.3	12.5	—
4	f	9/6	0	50	4/2	10.8	5 5	5.5
5	m	10/0	—1/6	<3	2/6	31.3	36.3	54.5
6	m	10/6	—0/6	10	7/6	59.–	25.0	23.6
7	f	11/4	0	85	3/6	13 0	—**	—
8	f	11/5	—3/6	<3	8/6	64 7	55 4	35 0
9	f	11/6	—0/6	25	1/0	11 0	30.0	5.5
10	f	12/0	0	8	4/0	28 0	21 0	21.3
11	m	12/0	—2/0	<3	6/0	45.6	30 0	35.9
12	m	12/4	—1	<3	5/1	13 7	30 0	30.0
13	f	13/0	0	10	3/0	18 8	23 1	16 8
14	f	13/1	0	10	1/0	6 9	20.7	13.0
15	m	13/6	0	<3	4/6	18.3	31 0	42.9
16	m	14/1	—1	40	7/5	42.8	12.5	12.5
17	f	15/4	0	50	3/0	21 8	10.0	—***

Treatment ended 4 months before investigation
**Treatment ended 16 months before investigation
***Treatment ended 6 months before investigation

1967) The diagnosis varied in all five patients and the results are, for several reasons, difficult to evaluate.

Material and methods

Subjects Seventeen children 6 to 15 years old and with steroid treatment for 1—8½ years were investigated. The reason for steroid treatment was in all patients asthma. All patients were in a good physical condition during the investigation and none had suffered a serious asthma attack during the week immediately preceding the study. The dosage of steroids varied during the last year of treatment but the mean dosage was calculated to allow a comparison with the growth increment during the year. Steroid preparations used were Prednisone, Prednisolone and Triamcinolone but all doses are calculated in Cortisone equivalents. (5 mg Prednisone/Prednisolone equal to 4 mg Triamcinolone equal to 25 mg Cortisone). Data about the patients are summarized in Table XXIV.

Insulin tolerance test The test was performed as described earlier (page 39) with the single exception that the last blood sample was withdrawn 75 minutes after the insulin injection.

Measurements of growth Regular control of standing height was performed 3—4 times a year. The height increments are compared with the whole year velocity standards for height of Tanner et al. (1966). Fig. 26 shows the height increments for case 13.

Bone age estimations were performed by the method of Eklöf and Ringertz (1967). The X-rays were all taken by a staff with long experience of the method, all calculations of the bone age were performed by the same radiologist.

Results

The results are summarized in Table XXV and illustrated in Fig. 27 showing a normal response (case 4) and an inhibited response

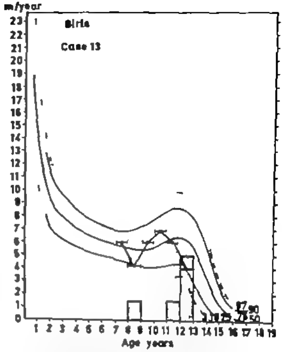

Fig. 26. Growth rate during steroid treatment. Shadowed areas indicate the dosing of Cortisone. A mean dose of 10, 10 and 23 mg Cortisone/day given during the year studied.

(case 11). In all patients the blood glucose dropped to less than 50 per cent of the resting level. Most patients showed minor discomfort during the hypoglycaemia (mild dizziness and sweating) but the test was not interrupted in any patient.

There was no difference in resting levels of growth hormone found between normal children (chapter XI) and children treated with steroids. The increase in growth hormone levels, however, was inhibited by the steroid treatment. There was a statistically significant difference ($p < 0.005$) for the HGH increments of normal children (29.1 ± 11.5 ng/ml) and those treated with corticosteroids (16.6 ± 8.2 ng/ml). There was no difference in time of growth hormone response since most patients showed maximal increment at 45 minutes, some already at 30 minutes and some at 60 minutes after the insulin gift.

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1	f	6/3	—3	<3	3/8	31.3	19.0	19.0
2	m	7/1	—1/3	<3	2/0	12.2	28.1	28.1
3	m	9/0	0	25	5/6	19.3	12.5	—
4	f	9/6	0	50	4/2	10.8	5.5	5.5
5	m	10/0	—1/6	<3	2/6	31.3	56.5	54.5
6	m	10/6	—0/6	10	7/6	59.2	25.0	23.6
7	f	11/4	0	85	3/6	13.0	—**	—
8	f	11/5	—3/6	<3	8/6	64.7	55.4	35.0
9	f	11/6	—0/6	25	1/0	11.0	30.0	5.5
10	f	12/0	0	8	4/0	28.0	21.0	21.3
11	m	12/0	—2/0	<3	6/0	45.6	30.0	35.9
12	m	12/4	—1	<3	5/1	13.7	30.0	30.0
13	f	13/0	[illegible]	10	3/0	18.8	23.1	16.8
14	f	13/1	[illegible]	10	1/0	6.9	20.7	13.0
15	m	13/6	[illegible]	<3	4/6	18.3	31.0	42.9
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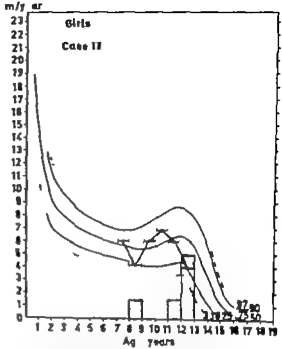

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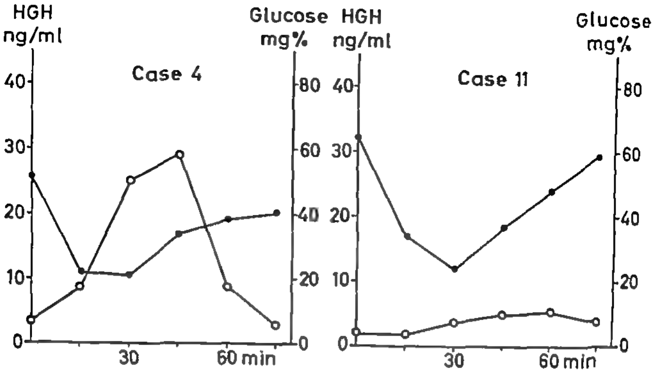

Fig 27 Blood glucose —• and HGH o—o response to insulin Normal response to the left inhibited response to the right

A correlation was sought between dosage of corticosteroids the month prior to the investigation and the maximal increment of HGH during insulin load. The result is shown in Fig 28 The correlation coefficient was —0 66 and the significance for the slope of the regression line to be different from 0 is at p <0 005 level. So there is a significant correlation between dosage of corticosteroids and increment in growth hormone during insulin load.

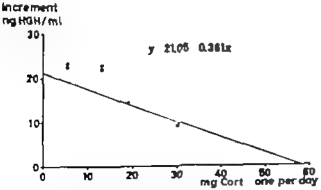

Fig 28 Correlation between increment of HGH during insulin load and dosage of Cortisone during the month prior to the study The line indicates the correlation line

It was possible to find a correlation between height increment percentile and growth hormone increase (Fig 29) The correlation coefficient is 0.52, and the significance for slope of the regression line to be different from 0 is at p <0 005 level. Yet it is very doubtful if this is a true correlation The height percentile is influenced by the steroid treatment of the previous year while the HGH increment on one occasion never can be representative for the whole year

Nothing is known about the duration of the inhibition of growth hormone release after the steroid therapy has finished and how temporal variations in steroid treatment influence the inhibition of growth hormone release. Some data indicate that the inhibition is of rather short duration If for instance instead of mean Cortisone dose during the last month the corresponding doses for the last three months are studied the correlation coefficient is about —0 32. Furthermore those patients (cases 3 and 17) who recently had finished their treatment showed normal increments. Case 9 having a very high Cortisone dosage (250 mg/day) two months

TABLE XXV *Growth hormone and blood glucose levels during IV insulin tolerance test in children with long-term treatment with corticosteroids*

Case	Mean Cortisone dosage last month, mg per day	Time in minutes Growth hormone levels in ng/ml Blood glucose levels in mg/100 ml 0	15	30	45	60	75
1	19	3.5 50	8.5 35	13 27	18 39	16 50	15 59
2	28	4.5 78	5.5 34	9 31	8 54	5.5 64	2.5 78
3	—	5 86	4.5 31	9 40	18 49	28 64	10 72
4	5.5	3.5 52	8.5 22	25 21	29 34	9 38	3 41
5	54.5	2 65	2 22	6 15	5 38	6 80	4 76
6	23.6	<1 69	1 34	1 23	8 58	5 73	4 69
7	—**	2 72	8.5 44	50 36	38 58	18 69	5 75
8	35	1 67	1 39	3 20	15 20	13 36	8 55
9	5.5	3.5 80	4.5 37	13 41	26 62	22 78	12 81
10	21.3	4 50	4 29	12 25	9 38	4 59	1 72
11	25.9	2 64	2 34	3 24	5 37	5 48	4 59
12	30	5.5 95	12 60	17 42	15 59	14 86	9 95
13	16.8	6 90	7 36	12 30	14 59	7.5 78	2 84
14	13	11 63	16 30	26 33	34 44	16 73	14 81
15	42.9	5 80	5.5 61	10 38	16 58	14 78	9 80
16	12.5	4 68	3.5 32	19 38	25 51	22 63	18 65
17	—***	7 82	10 47	35 37	33 33	27 72	25 78

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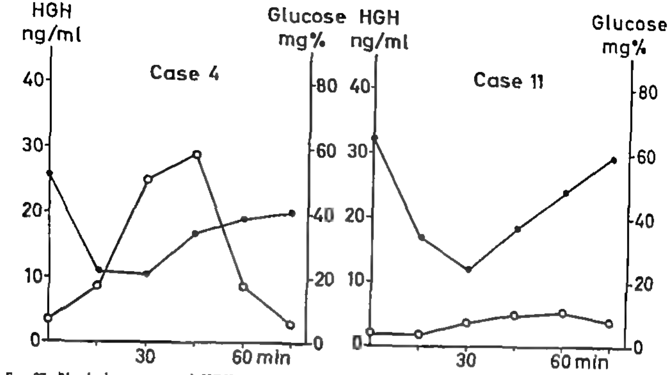

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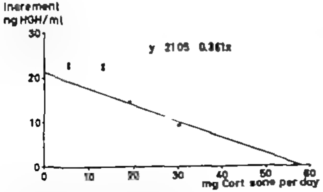

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decreased range in normal variation in the technique used by Root et al. will hide the moderate inhibition that would be expected for the comparably low dosage of corticosteroids used in the four patients in which no inhibition could be noted. In accordance with the previous findings of Frantz and Rabkin (1964) and Hartog et al. (1964 b) on adults, the results of the present study show that corticosteroids inhibit the release of growth hormone during insulin-induced hypoglycaemia even in children. The degree of inhibition is correlated to the amount of steroids.

At this time, however little is known about the mechanism of the inhibition of the pituitary function by the corticosteroids. Vernikos-Danellis (1965) has studied the corticotrophic function in rats and was able to show that Cortisone reduced the corticotrophin-releasing factor (CRF) of the median eminence in the hypothalamus. Furthermore it was shown that a dose of corticosteroids that was sufficient to inhibit stress-induced ACTH release did not affect the pituitary ACTH content. Whether the suppression is caused by influence on the regulatory system of the hypothalamus or on the synthesis of CRF is unknown.

Corresponding studies in the same animal for GH have been performed by Pecile and Müller (1966) who could show that the content of GH in the anterior pituitary was influenced by corticosteroids, whereas the amount of growth hormone releasing factor was decreased. Thus even for GH the inhibition seems to be due to some changes in the neurohumoral structures of the hypothalamus. This is in agreement with the findings of Abrams et al. (1964) who demonstrated an impairment in GH response to hypoglycaemia in squirrelmonkeys with hypothalamic lesions and with the results of Roth et al. (1963 a) who, in a patient subjected to pituitary stalk section, found that the usual response to hypoglycaemia was inhibited despite normal resting levels of growth hormone.

In most children with long term steroid treatment a retardation of the start of puberty is noted. An attractive explanation for this is inhibition in further neurohumoral functions in the hypothalamic region caused by the steroids.

Resting levels of HGH are normal even in steroid treated children and the inhibition of HGH release during hypoglycaemia, a rather unphysiological state, is not proof that this inhibition is the only or the main reason for the reduced growth in these children. Probably the effect of steroids on the hypothalamic structures is one of several factors that cause the inhibition of growth. One factor could be the katabolic action of corticosteroids *per se* resulting in a supply of protein insufficient for adequate growth. The delay in bone age could support this. Of great interest are the results of Friedman and Strang (1966) who found that the growth impairment caused by corticosteroids could be diminished if the patients were treated with a combination of corticosteroids and corticotrophin. Converting the total amount of corticosteroids to corticotrophin did enhance rather than inhibit growth. Since ACTH *per se* does not stimulate HGH secretion, the authors suggest other presently unknown adrenal steroids released by ACTH to be growth promoting factors. Several substances as yet not specifically characterised, but with typical steroid color reactions have been found in adrenal venous blood of dogs (Farrel and Lamus 1953). In practice it would look attractive to replace treatment with corticosteroids with ACTH. However only ACTH of animal origin is avialable and it has to be given in injections. Allergic reactions have been reported but are less common when highly purified ACTH is used. A synthetic α1—24-corticotrophin (Synacten® Ciba) has been introduced and this might eliminate the risk for allergic side-reactions. It would be of interest to study growth hormone increments in children treated with corticotrophin.

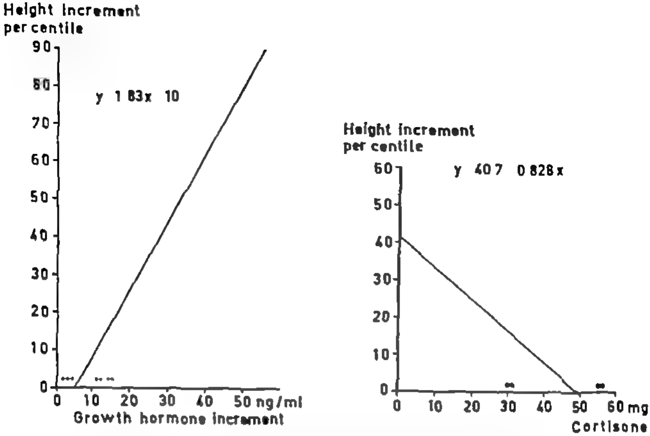

Fig 29 Correlation between height increment percentile and HGH response to insulin-induced hypoglycaemia to the left and correlation between height increment percentile and mean Cortisone dose per day during the actual year to the right. The lines indicate correlation lines

before the investigaion and a moderate dosage at the time of the experiment, shows normal growth hormone increment. It is also noted that growth inhibition is decreased if the corticosteroids are given intermittently

It would be of interest to try to correlate the mean dosage of Cortisone during the last year with the height increment during that time. This is shown in Fig. 29 The correlation coefficient is —0 68 and the significance for the slope of the regression line to be different from 0 is at p <0 005 level Furthermore it is noted that those patients who have got a mean Cortisone dosage of more than 20 mg per day during the current year have a height increment percentile of 10 or less.

The bone age was delayed in 9 of the 17 patients. Roughly all patients with delay in bone age have had a mean Cortisone dose of 7 g or more per year One patient, however (case 12) shows a moderate delay in bone age with only 2.7 g Cortisone/year another patient (case 17) got 7.3 g per year without retardation of the bone age. However that patient was 15 years old and had finished her steroid treatment six months before the X ray for the bone age determination.

Discussion

The results of the present study are not in agreement with those found in children by Root et al (1967) who were not able to show any inhibition in growth hormone release during insulin induced hypoglycaemia in four of their five Cortisone-treated patients. Results of the method of Root et al (1967) differ from the results of other methods in the measurement of HGH response to hypoglycaemia in normal children, as well. The reason for this has been discussed earlier (page 40) It is supposed that the

decreased range in normal variation in the technique used by Root et al. will hide the moderate inhibition that would be expected for the comparably low dosage of corticoster oids used in the four patients in which no inhibition could be noted. In accordance with the previous findings of Frantz and Rabkin (1964) and Hartog et al. (1964 b) on adults, the results of the present study show that corticosteroids inhibit the release of growth hormone during insulin-induced hypoglycaemia even in children. The degree of inhibition is correlated to the amount of steroids.

At this time, however little is known about the mechanism of the inhibition of the pituitary function by the corticosteroids. Vernikos-Danellis (1965) has studied the corticotrophic function in rats and was able to show that Cortisone reduced the corticotrophin releasing factor (CRF) of the median eminence in the hypothalamus. Furthermore it was shown that a dose of corticosteroids that was sufficient to inhibit stress-induced ACTH release did not affect the pituitary ACTH content. Whether the suppression is caused by influence on the regulatory system of the hypothalamus or on the synthesis of CRF is unknown.

Corresponding studies in the same animal for GH ha e been performed by Pecile and Muller (1966) who could show that the content of GH in the anterior pituitary was influenced by corticosteroids, whereas the amount of growth hormone-releasing factor was decreased. Thus even for GH the inhibition seems to be due to some changes in the neurohumoral structures of the hypothalamus. This is in agreement with the findings of Abrams et al. (1964) who demonstrated an impairment in GH response to hypoglycaemia in squirrelmonkeys with hypothalamic lesions and with the results of Roth et al. (1963 a) who, in a patient subjected to pituitary stalk section, found that the usual response to hypoglycaemia was inhibited despite normal resting levels of growth hormone.

In most children with long term steroid treatment a retardation of the start of puberty is noted. An attractive explanation for this is inhibition in further neurohumoral functions in the hypothalamic region caused by the steroids.

Resting levels of HGH are normal even in steroid treated children and the inhibition of HGH release during hypoglycaemia, a rather unphysiological state, is not proof that this inhibition is the only or the main reason for the reduced growth in these children. Probably the effect of steroids on the hypothalamic structures is one of several factors that cause the inhibition of growth. One factor could be the katabolic action of corticosteroids *per se* resulting in a supply of protein insufficient for adequate growth. The delay in bone age could support this. Of great interest are the results of Friedman and Strang (1966) who found that the growth impairment caused by corticosteroids could be diminished if the patients were treated with a combination of corticosteroids and corticotrophin. Converting the total amount of corticosteroids to corticotrophin did enhance rather than inhibit growth. Since ACTH *per se* does not stimulate HGH secretion, the authors suggest other presently unknown adrenal steroids released by ACTH to be growth promoting factors. Several substances as yet not specifically characterised, but with typical steroid color reactions have been found in adrenal venous blood of dogs (Farrel and Lamus 1953). In practice it would look attractive to replace treatment with corticosteroids with ACTH. However only ACTH of animal origin is avialable and it has to be given in injections. Allergic reactions have been reported but are less common when highly purified ACTH is used. A synthetic α1—24-corticotrophin (Synacten[R] Ciba) has been introduced and this might eliminate the risk for allergic side-reactions. It would be of interest to study growth hormone increments in children treated with corticotrophin.

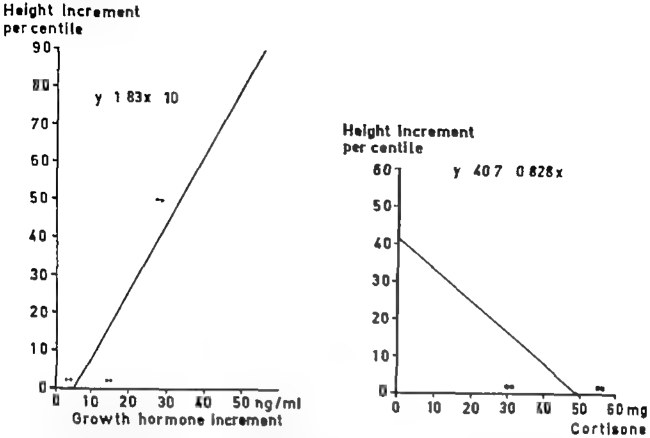

Fig 29 Correlation between height increment percentile and HGH response to insulin-induced hypoglycaemia to the left and correlation between height increment percentile and mean Cortisone dose per day during the actual year to the right The lines indicate correlation lines.

before the investigaion and a moderate dosage at the time of the experiment, shows normal growth hormone increment. It is also noted that growth inhibition is decreased if the corticosteroids are given intermittently

It would be of interest to try to correlate the mean dosage of Cortisone during the last year with the height increment during that time. This is shown in Fig 29 The correlation coefficient is —0 68 and the significance for the slope of the regression line to be different from 0 is at p <0 005 level. Furthermore it is noted that those patients who have got a mean Cortisone dosage of more than 20 mg per day during the current year have a height increment percentile of 10 or less.

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Growth hormone levels during the first week of life in full term normal infants infants of diabetic mothers and in premature infants

Several authors have reported high levels of growth hormone during the neonatal period (Cornblath et al. 1965 Laron et al. 1966 and Milner and Wright 1966) However most of the data are single determinations on different patients during the actual period. Differences have been shown between premature and full-term infants (Cornblath et al. 1965) and between normal infants and infants of diabetic mothers (Laron et al. 1967) The effect on HGH levels during insulin or glucose load has been reported in isolated cases. Milner and Wright (1966) have reported the growth hormone response to hyperglycaemia induced by exchange transfusion with glucose and disodium citrate used as preservative in twentytwo cases. However exchange transfusions induce many other metabolic changes in the blood so the results are difficult to evaluate. In this study full-term normal infants and infants of diabetic mothers have been studied with insulin and glucose load during the first week of life. In addition, a small group of premature infants will be presented.

Material and methods

Data about the patients studied are shown in Table XXVI Prematurity is defined as birth weight below 2,500 g.

All infants were well at time of the study The reason for the caesarean section in the control infants was threatening obstetrical complications. There was no prolonged labor prior to the operation. The infants of diabetic mothers were routinely delivered by caesarean section.

For the study the umbilical vein was catheterized with a small polyethylene tube (Bardic[R] infant feeding tube. C. R Bard, Inc., Murray Hill U.S.A.) Blood samples were obtained from the tube and placed in glass tubes containing heparin (Vitrum, Stockholm, Sweden) Blood for glucose estimation was withdrawn immediately The samples were kept at +4 C until centrifuged. The plasma was withdrawn and frozen. To prevent clotting in the polyethylene tube 2 ml of 0.9 % saline with 10 U heparin per ml was injected after the blood sample was drawn. The first 1 ml containing blood, saline and heparin was discarded at each time interval before a blood sample was obtained.

Hypoglycaemia was induced by giving insulin intravenously through the plastic tube in a dose of 4 U/square meter body surface. A blood sample was drawn prior to the insulin load and the insulin was followed by 5 ml of 0 9 % saline. Then the polyethylene tube was replaced by a new one to avoid contamination. Blood samples were drawn every 15 minutes until 105 or 120 minutes after the insulin injection except for some of the prematures where it was impossible to withdraw such large volumes of blood.

Hyperglycaemia was induced by the injection of 0.5 g glucose/kg body weight in 15 % solution. The same precaution of changing the polyethylene tube was taken. Blood samples were collected prior to the glucose injection and at time intervals as above after injection.

The combined insulin-glucose-load was started as an ordinary insulin load, a blood sample was drawn 70 minutes after the insu-

Summary

The growth hormone increment induced by hypoglycaemia has been studied in 17 children treated with corticosteroids. No difference in fasting levels was found between normal children and Cortisone-treated children. An inhibition in HGH release due to insulin induced hypoglycaemia was found as well as a correlation between the inhibition of HGH release and dosage of corticosteroids. Furthermore a correlation between mean dose of corticosteroids per year and height increment was observed. The bone age was delayed in nine of the children all of them having high doses of steroids. The mode of the inhibition to HGH release is discussed. Reduced growth is most likely due as well to factors other than inhibition of HGH release. Despite the disadvantage in method of administration, ACTH might be tried more frequently

Growth hormone levels during the first week of life in full term normal infants, infants of diabetic mothers and in premature infants

Several authors have reported high levels of growth hormone during the neonatal period (Cornblath et al. 1965 Laron et al. 1966 and Milner and Wright 1966) However most of the data are single determinations on different patients during the actual period. Differences have been shown between premature and full-term infants (Cornblath et al. 1965) and between normal infants and infants of diabetic mothers (Laron et al. 1967) The effect on HGH levels during insulin or glucose load has been reported in isolated cases. Milner and Wright (1966) have reported the growth hormone response to hyperglycaemia induced by exchange transfusion with glucose and disodium citrate used as preservative in twentytwo cases. However exchange transfusions induce many other metabolic changes in the blood so the results are difficult to evaluate. In this study full-term normal infants and infants of diabetic mothers have been studied with insulin and glucose load during the first week of life. In addition, a small group of premature infants will be presented.

Material and methods

Data about the patients studied are shown in Table XXVI. Prematurity is defined as birth weight below 2,500 g.

All infants were well at time of the study The reason for the caesarean section in the control infants was threatening obstetrical complications. There was no prolonged labor prior to the operation. The infants of diabetic mothers were routinely delivered by caesarean section.

For the study the umbilical vein was catheterized with a small polyethylene tube (Bardic[R] infant feeding tube. C. R. Bard, Inc., Murray Hill, U.S.A.) Blood samples were obtained from the tube and placed in glass tubes containing heparin (Vitrum, Stockholm, Sweden) Blood for glucose estimation was withdrawn immediately The samples were kept at +4 C until centrifuged. The plasma was withdrawn and frozen. To prevent clotting in the polyethylene tube 2 ml of 0.9 °/o saline with 10 U heparin per ml was injected after the blood sample was drawn. The first 1 ml containing blood, saline and heparin was discarded at each time interval before a blood sample was obtained.

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Hyperglycaemia was induced by the injection of 0.5 g glucose/kg body weight in 15 °/o solution. The same precaution of changing the polyethylene tube was taken. Blood samples were collected prior to the glucose injection and at time intervals as above after injection.

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buffer flow chromatography 25 µl of 7 % bovine serum albumin in 0.9 % saline was added to keep constant the amount of carrier protein in the buffer flow. For the standard curve 50 µl of a mixture of equal parts heparinized plasma from blood donors and albumin as above was added.

Results

The results are shown in Fig. 30—34 and summarized in Table XXVII. Statistical evaluation of the different HGH release determinations is shown in Tables XXVIII, XXIX and XXXI.

The hypoglycaemia induced by insulin was more pronounced in infants of diabetic mothers. Slightly lower levels were noticed during the first day of life for all groups of patients when compared to the end of the first week. The fall in blood glucose from the basic level was of about the same degree on both occasions studied and in all patients (Fig. 35).

The base levels of HGH are, for all patients studied, higher during the first day of life than at the age of 5—6 days. The base levels of infants of diabetic mothers are markedly lower than those of other groups. The decrease between the first day of life and the age of 5—6 days is less marked in premature infants.

TABLE XXVII *Serum growth hormone levels in different groups of patients Mean and range of resting levels and peak levels*

			HGH in ng/ml			
Group of patients	No. of patients	Age	Mean ± S.D base levels	Range	Mean ± S.D levels 45 min.	Range
Normal infants caesarean section	9	5—24h	79.2 ± 8.5	70—90	159.7 ± 23.1	128—90
		5—6 d.	44.0 ± 8.9	32—60	91.6 ± 10.8	76—110
Infants of diabetic mothers	9	5—24h	47.8 ± 4.0	38—62	84.1 ± 15.1	65—110
		5—6 d.	28.4 ± 6.6	22—37	43.6 ± 6.6	32—65
Normal infants spontaneous delivery insulin load	3	5—24h	82.3 ± 9.7	72—90	162.7 ± 20.1	148—178
		5—6 d.	35.7 ± 7.3	28—43	76.7 ± 9.2	68—87
Normal infants spontaneous delivery glucose load	3	5—24h	81.0 ± 4.3	78—86	177.0 ± 18.2	165—198
		5—6 d.	31.0 ± 4.0	27—35	76.3 ± 26.8*	62—84*
Premature infants insulin load	3	5—24h	77.0 ± 14.1	64—92	190.3 ± 6.2	186—193
		5—6 d.	60.7 ± 3.4	56—64	198.0 ± 10.1	188—210
Premature infants glucose load	2	5—24h	79.5 ± 2.5	77—82	176.0 ± 26.8*	157—195
		5—6 d.	50.5 ± 3.5	48—53	152.0 ± 15.5	141—157*

Indicates results at 60 min., since highest levels were obtained at that time.

TABLE XXVI *Clinical data about the patients*

Case number	Sex	Birth-weight, g	Length, cm	Gestation, weeks	Group of patients	Delivery	Investigation performed
1	f	3580	49	40	normal infant	caesarean section	
2	m	3210	49	39			insulin load
3	m	2560	46	38			
4	f	2740	47	39			
5	f	3860	51	40			
6	m	3170	50	40			
7	m	3370	50	38			
8	m	3030	48	38			combined insulin-glucose load
9	m	3910	[illegible]	41			
10*	f	3860	51	38			
11	f	2530	47	36	infant of diabetic mother		
12	f	3550	50	37			
13	m	2560	47	36			
14	m	3390	50	36			
15	f	2990	46	37			
16	m	3800	48	36			
17	m	2570	44	36			
18	f	2860	47	36			
19	f	3010	46	36			
20	f	2980	48	38	normal infant	spontaneous	insulin load
21	m	3570	51	40			
22	m	3910	52	40			
23	m	2750	47	38			glucose load
24	f	3100	49	41			
25	f	3880	50	40			
26	f	1570	41	33	premature		insulin load
27	m	1690	43	33			
28	f	2430	46	36			
29	f	1810	44	34			glucose load
30	m	2160	45	35			

*The results obtained show that the patient should be classified as an infant of a mother with gestational diabetes.

lin injection, followed by 0.5 g glucose/kg of body weight within 1 minute. The polyethylene tube was replaced by a new tube and blood samples were collected at 5, 20 and 35 minutes after the glucose gift.

The first investigation was performed between 5—24 hours of age and a second on the same patient at the age of 5—6 days. The age of the infant is the time (hours or days) that has passed since the delivery. The infants were starving before the first investigation and had been fasting about 4 hours prior to the second. To prevent infection the infants got Ampicillin[R] in doses of 50 mg/kg and day for 5 days after each umbilical catheterization. Most infants got a small transfusion of blood after the second investigation. No complications to the study have been observed. During the study the temperature of the infant decreased slightly. The decrease, however, did not exceed 1°C.

Blood glucose was estimated by a modification of the glucoseoxidase method using 0.025 M NaOH and 10 % $ZnSO_4—7\ H_2O$ as protein precipitating agents. (*Hjelm* and de Verdier 1963.)

Radioimmunoassay of growth hormone was performed by the method described in Part I with one exception. Since rather high levels of growth hormone were expected the amount of plasma in the incubation mixture was reduced from 50 µl to 25µl. Prior to the

buffer flow chromatography 25 µl of 7 % bovine serum albumin in 0.9 % saline was added to keep constant the amount of carrier protein in the buffer flow. For the standard curve 50 µl of a mixture of equal parts heparinized plasma from blood donors and albumin as above was added.

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23	m	2750	47	38			glucose load
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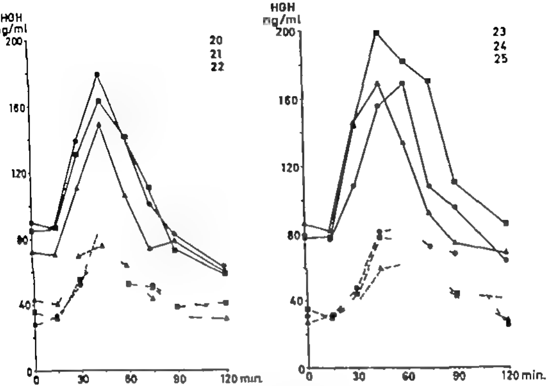


Fig. 32 Growth hormone levels during insulin load (to the left) and glucose load (to the right) on the first day of life —— and at the age of 5—6 day - - - in 6 normal full-term infants delivered spontaneously. Characters refer to table XXVI

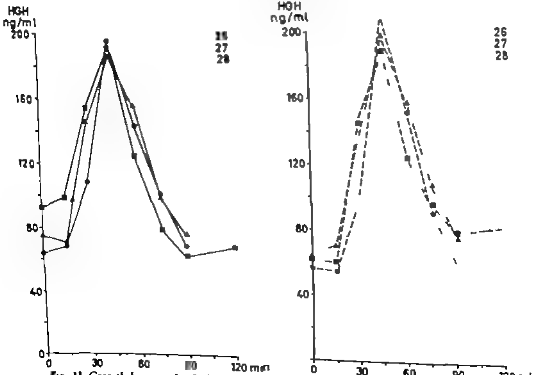


Fig. 33 Growth hormone levels during insulin load in the first day of life —— and at the age of 5—6 day - - - in 3 premature infants. Characters refer to Table XXVI

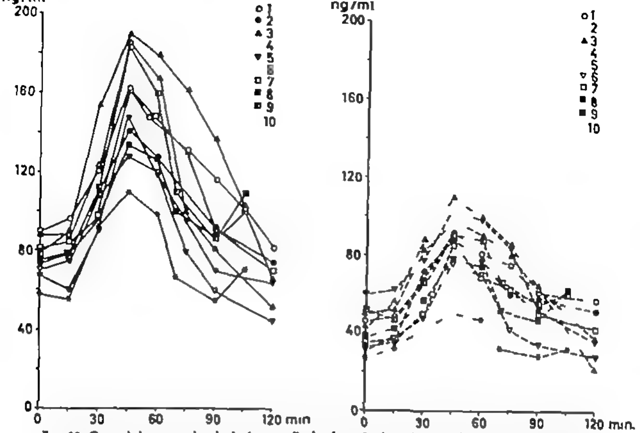


Fig 30 Growth hormone levels during insulin load on the first day of life —— and at the age of 5—6 days ---- in 10 normal full-term infants delivered by caesarean section. Characters refer to Table XXVI. A combined insulin glucose load was performed on cases 8, 9 and 10, the glucose being injected immediately after withdrawal of the blood sample at 70 minutes.

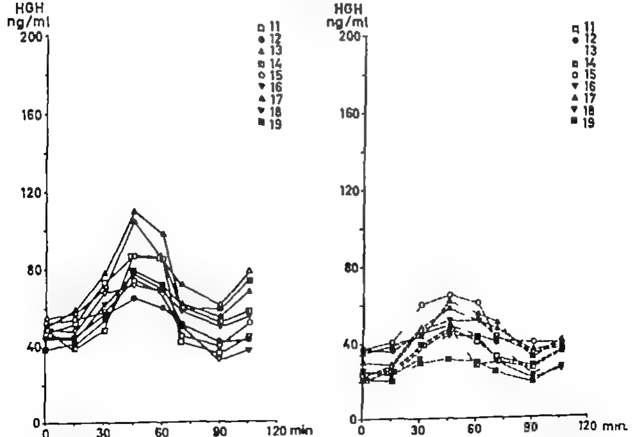


Fig 31 Growth hormone levels during combined insulin- glucose load on the first day of life —— and at the age of 5—6 days ---- in 9 infants of diabetic mothers. The glucose was injected immediately after withdrawal of the blood sample at 70 minutes. Characters refer to Table XXVI

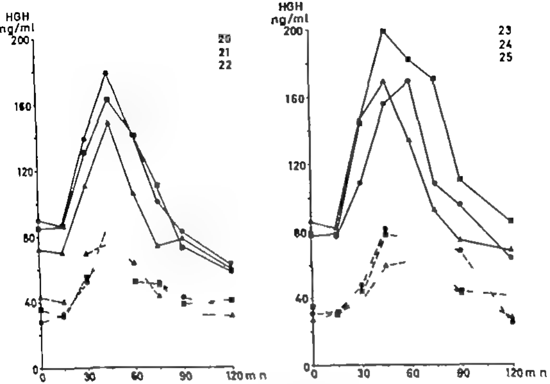


Fig. 32 Growth hormone levels during insulin load (to the left) and glucose load (to the right) on the first day of life —— and at the age of 3—6 days ---- in 6 normal full-term infants delivered spontaneously. Characters refer to table XXVI

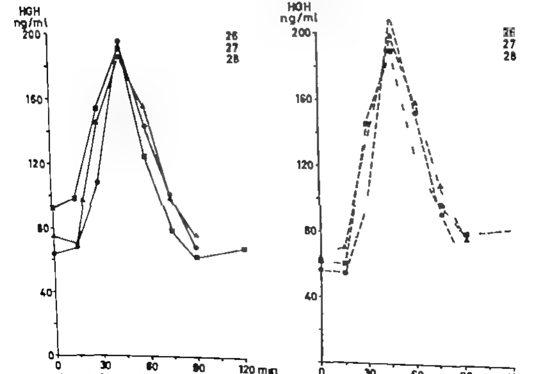


Fig. 33 Growth hormone levels during insulin load in the first day of life —— and at the age of 5—6 days ---- in 3 premature infants. Characters refer to Table XXVI

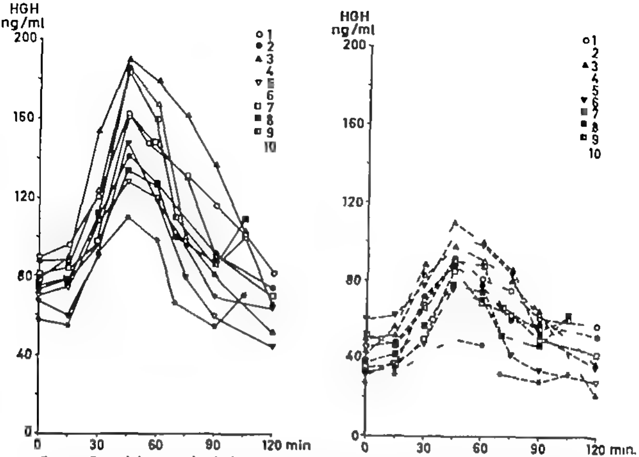
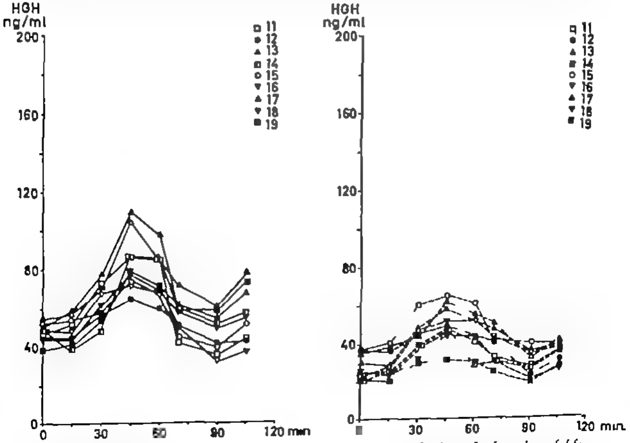


Fig. 30. Growth hormone levels during insulin load on the first day of life —— and at the age of 5—6 days in 10 normal full-term infants delivered by caesarean section. Characters refer to Table XXVI. A combined insulin- glucose load was performed on cases 8, 9 and 10, the glucose being injected immediately after withdrawal of the blood sample at 70 minutes.



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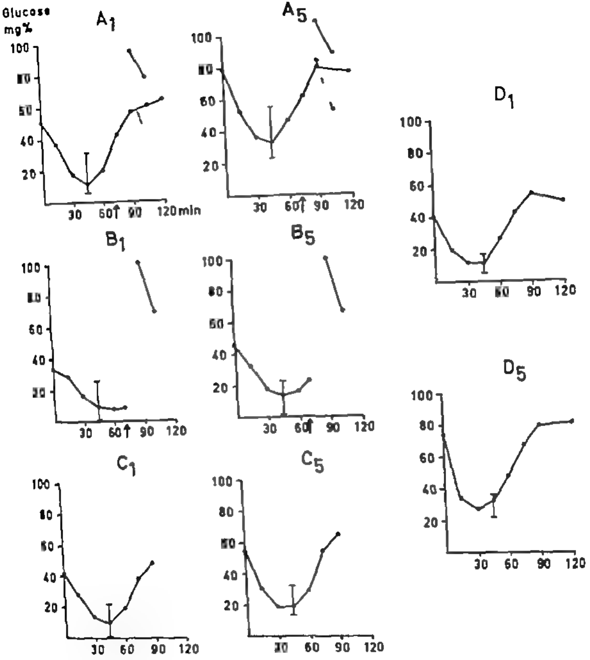

Fig 35 Mean of blood glucose during insulin loads. Bars indicate range of lowest levels. The characters 1 and 5 refer to the age 1 and 5—6 days respectively. The letter A—D refer to the following groups: A Normal infants, insulin load exc pt for 3 patients with combined insulin-glucose load. ↓ Indicates case 10
B Infants of diabetic mother
C. Normal infants delivered spontaneously
D Premature infants.

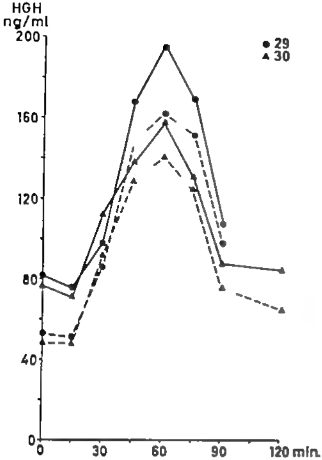

Fig 34 Growth hormone levels d ring glucose load in the first day of life —— and at the age of 5—6 days - - - in 2 premature infants Characters refer to Table XXVI

The HGH increase due to hypoglycaemia was, when expressed in absolute levels, considerably greater in the first day of life than at the end of the first week for all patients except for the premature infants. The increase was more pronounced in normal and premature infants than in infants of diabetic mothers (Table XXVIII)

If instead of absolute values of HGH, the per cent maximal increment from the basic levels at the start of the experiment are compared, this increase seems to be of about the same degree for all patients except for the premature infants. These 3 patients increased their increment at the end of the first week when compared to the first day of life. The statistical evaluation is summarized in Table XXIX

The effect of hyperglycaemia was studied in two different experiments which makes it difficult to compare the patients. The blood glucose levels in the single glucose loads are shown in Fig 36 The glucose disappearance rate (K_G)* is shown in the figure. It is slightly higher for normal infants than for prematures In the infants of diabetic mothers the glucose load was added to the insulin load and this was also performed on three normal infants. The rate of glucose disappearance (k_G) for these patients is summarized in Table XXX.

The HGH levels increased during hyperglycaemia in all patients, the increase in absolute levels being more pronounced during the first day of life. The increase was higher for premature infants at the end of the first week than for normal infants. Statistical evaluation is shown in the upper part of Table XXXI If instead of increase in absolute levels the per cent maximal increment is studied the increase seems to be more pronounced at the end of the first week for prematures while other patients studied do not show any difference. The statistical evalution is shown in the lower part of Table XXXI

Of special interest is case number 10 Her HGH levels during the whole study are in better agreement with those of infants of diabetic mothers than with those of normal infants. She is the second child of the mother the first child having a birth weight of 4 680 g A glucose tolerance test on the mother one month after delivery of the first child showed a glucose disappearance rate (k_G) of 1 01

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* k_G accordi g to the method f Hamilton and Stein (1942) a mod fied by Ikkos and Luft (1957).

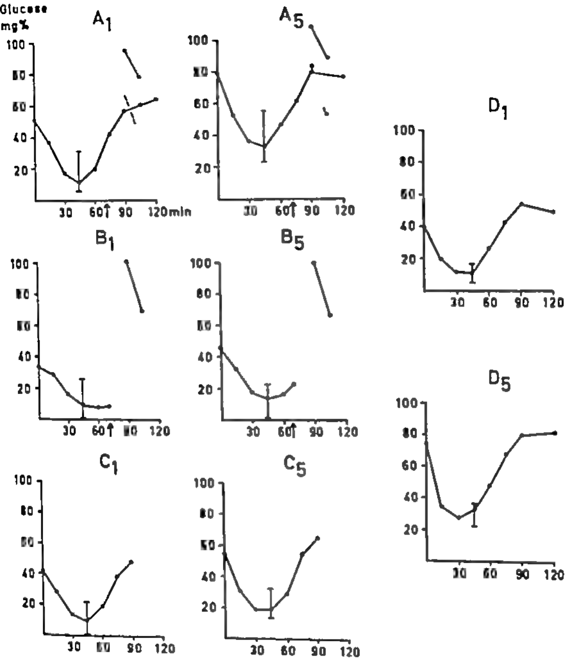

Fig. 35. Mean of blood glucose during insulin load. Bar indicate range of lowest levels. The character 1 and 5 refer to the age 1 and 5—6 days respectively. The letters A—D refer to the following group:
A Normal infants, insulin load except for 3 patient with combined insulin-glucose load ... *ates 10*
B Infant of diabetic mother
C Normal infants delivered spontaneously
D Premature infant

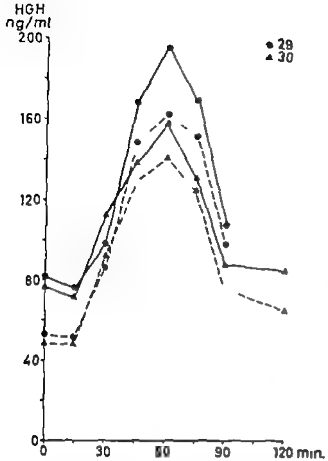

Fig 34 Growth hormone levels during glucose load in the first day of life —— and at the age of 5—6 days in 2 premature infants Characters refer to Table XXVI

The HGH increase due to hypoglycaemia was, when expressed in absolute levels, considerably greater in the first day of life than at the end of the first week for all patients except for the premature infants. The increase was more pronounced in normal and premature infants than in infants of diabetic mothers (Table XXVIII)

If instead of absolute values of HGH the per cent maximal increment from the basic levels at the start of the experiment are compared, this increase seems to be of about the same degree for all patients except for the premature infants. These 3 patients increased their increment at the end of the first week when compared to the first day of life. The statistical evaluation is summarized in Table XXIX.

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* k_G according t th method f Hamilton and Stern (1942) modified by Ikkos and L ft (1957)

The glucose disappearance rate (k_G) for case 10 is shown in Table XXX. The high k_G value for patient 10 and for infants of diabetic mothers is in agreement with the results published by Gentz et al. (1967) and is a further support for the suspicion that case 10 should be classified as child of mother with gestational diabetes. This patient has therefore been excluded from the normal infants in the statistical evaluations.

TABLE XXVIII. *Significance tests for HGH response to insulin-induced hypoglycaemia. Absolute levels at all time-intervals studied. IDM stands for infants of diabetic mothers*

Groups of infants compared			p-value
Normal 1st day	>	Normal 5—6 days	<0.001
IDM 1st day	>	IDM 5—6 days	<0.001
Normal 1st day	>	IDM 1st day	<0.001
Normal 5—6 days	>	IDM 5—6 days	<0.001 except 70 min. p <0.01
Premat. 5—6 days	>	Normal 5—6 days	<0.005 except 15 min. p <0.03**

* Differences for each patient is compared by Student's t-test for paired samples at all time intervals studied.
** Mean level of HGH for each time interval studied in one group is compared by Student's t-test for non-paired samples with corresponding level of the other group.

TABLE XXIX. *Significance tests for HGH response to insulin-induced hypoglycaemia. Per cent increment of base level is compared. In the upper part of the table no statistically significant differences are present in contrast to the lower part. IDM stands for infants of diabetic mothers*

Groups of infants compared			p-value
Normal 1st day	>	Normal 5—6 days	>0.2*
IDM 1st day	>	IDM 5—6 days	>0.2*
Normal 1st day	>	IDM 1st day	>0.1**
Normal 5—6 days	>	IDM 5—6 days	>0.05**
Normal 1st day	>	Premat. 1st day	>0.1**
Premat. 5—6 days	>	Premat. 1st day	<0.025
Premat. 5—6 days	>	Normal 5—6 days	<0.001**

* and ** see Table XXVIII

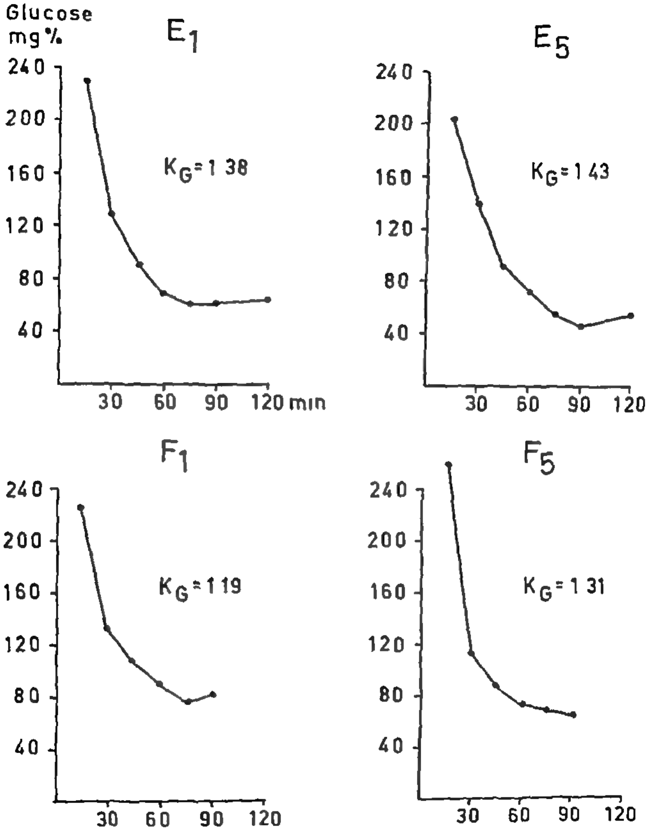

Fig. 36. Mean of blood gluc se during glucose load in the fi st day (1) and at the age of 5—6 d ys (5). F P ematurc infants. The K ... c lculated as stated on page 68

The glucose disappearance rate (k_G) for case 10 is shown in Table XXX. The high k_G value for patient 10 and for infants of diabetic mothers is in agreement with the results published by Gentz et al. (1967) and is a further support for the suspicion that case 10 should be classified as child of mother with gestational diabetes. This patient has therefore been excluded from the normal infants in the statistical evaluations.

TABLE XXVIII. *Significance tests for HGH response to insulin-induced hypoglycaemia. Absolute levels at all time-intervals studied. IDM stands for infants of diabetic mothers*

Groups of infants compared			p- alue
Normal 1st day	>	Normal 5—6 day	<0.001
IDM 1st day	>	IDM 5—6 days	<0.001
Normal 1st day	>	IDM 1st day	<0.001
Normal 5—6 days	>	IDM 5—6 days	<0.001 except 70 mi p <0.01
Premat 5—6 days	>	Normal 5—6 days	<0.025, ex ept 15 min. p <0.03

Differences for each patient compared by Student test for p ed samples ll time intervals studied.
**Mean level of HGH for each time interval studied in on group as compared by S udent test for non-paired samples w h corresponding level of the other group

TABLE XXIX. *Significance tests for HGH response to insulin induced hypoglycaemia. Per cent increment of base level is compared. In the upper part of the table no statistically significant differences are present in contrast to the lower part. IDM stands for infants of diabetic mothers*

Groups of infants compared			p- lue
Normal 1st day	>	Normal 5—6 days	>0.2*
IDM 1st day	>	IDM 5—6 days	>0.2*
Normal 1st day	>	IDM 1st day	>0.1**
Normal 5—6 days	>	IDM 5—6 days	>0.08**
Normal 1st day	>	Premat. 1st day	>0.1
Premat. 5—6 days	>	Premat. 1st day	<0.025
Premat. 5—6 days	>	Normal 5—6 days	<0.001**

* and ** see Table XXVIII

TABLE XXX. *Glucose disappearance in combined insulin glucose load The values are calculated from the glucose levels 20 and 35 minutes after the glucose gift IDM stands for infants of diabetic mothers*

Group of infants	No of patients	Ag	K_G
Normal infants	2	1 st day	1.32
Normal infants	2	5—6 days	1 46
IDM	9	1st day	2.51
IDM	9	5—6 days	2.75
Patient no 10		1st day	3.51
Patient no 10		5—6 days	3.29

TABLE XXXI *Significance tests for HGH response to hyperglycaemia Absolute levels at all time intervals studied are presented in the upper part Per cent increment of base level is compared in the lower part IDM stands for infants of diabetic mothers*

Groups of infants compared			p-value
Normal 1 st day	>	Normal 5—6 days	<0.001
IDM 90 min 1st day	<	IDM 105 min 1st day	<0.001
IDM 90 min. 5—6 days	<	IDM 105 min 5—6 days	<0.001
Premat. 5—6 days	>	Normal 5—6 days	<0.025 except fo 90 mi p <0.1**
Normal 1 st day	>	Normal 5—6 days	>0 2
IDM 1st day	>	IDM 5—6 days	>0.7*
Normal 1st day	>	Premat. 1 st day	>0.1
Premat. 5—6 day	>	Premat 1 st day	<0 05
Premat. 5—6 days	>	Normal 5—6 days	<0.025

and se Table XXVIII

Discussion

The paucity of data on HGH levels in the neonatal period and the wide variations in individual HGH response make the evaluation of the results difficult

The high base levels during the first day of life were initially believed to depend on placental transfer of human placental lactogen (HPL) a substance with hormonal activity present in maternal serum in amounts that at term are about 1 000 times those of HGH (Kaplan and Grumbach 1963) HPL crossreacts to some degree with HGH antiserum and would in part be measured in the immunoassay as HGH. However Beck et al (1965) have shown with a specific immunoassay for HPL that cord blood contains hardly measurable amounts of HPL.

Studies of HGH response to hypoglycaemia have been performed earlier in only four normal infants and two premature infants during the first day of life (Cornblath et al 1965)

The results are in agreement with those found in the present study. No infants of diabetic mothers have been studied and it is interesting that gestational diabetes seems to provoke changes in HGH response similar to those found in infants of diabetic mothers.

Hyperglycaemia has been studied in eight infants with a continuous glucose infusion (Cornblath et al. 1965) and during exchange transfusion by Milner and Wright (1966). Thus the experiments are not quite comparable. However all studies have shown an increase in HGH levels to hyperglycaemia during the neonatal period contrary to the findings at the age of 15 days or more (Cornblath et al. 1965).

The role of growth hormone during the neonatal period is not clearly understood. It does not seem to be indispensable as a growth promoting factor during the neonatal period since anencephalic human infants, even when born without a pituitary gland, have large, well-proportioned bodies (Seckel 1960). Furthermore the administration of growth hormone in premature infants does not accelerate the bone growth (*Chiumello et al. 1965*).

The *finding that HGH levels in newborn infants are higher than those of the mother* (Laron et al. 1966) *indicate an active secretion of hormone by the foetus.* Kaplan and Grumbach (1962) have demonstrated growth hormone in the pituitary gland of a 15 week foetus. The disappearance of growth hormone was studied (Cornblath et al. 1965) by *intra*venous administration of the hormone to newborn infants. The average $T^{1}/_{2}$ was 12.7 minutes compared with about 25—30 minutes for adults (page 29). So the high values obtained during the neonatal period are not due to slower plasma clearance.

For adults the main function of growth hormone seems to be homeostasis of energy providing substrates by its lipolytic action. If the energy requirements can be met by carbohydrates, secretion of growth hormone is not demanded. Glick et al. (1965) demonstrated that the normal prompt rise in HGH to insulin induced hypoglycaemia was prevented by a simultaneous administration of glucose. The subsequent fall in blood glucose after glucose administration led to a rise in HGH which was correlated in time with the secondary rise in plasma free fatty acids (FFA) after an oral glucose load. (Bolinger et al. 1962). There is no correlation between the absolute levels of blood glucose and growth hormone secretion since even very small changes in blood glucose induced by infusion of small amounts of insulin over an hour causes a marked rise in plasma HGH (Luft et al. 1966). Prolonged fasting, particularly in conjunction with exercise, increases the growth hormone levels (Hunter and Rigal 1966). Even here the effect of growth hormone will be energy homeostasis by lipolysis.

The intravenous administration of large amounts of some amino-acids, particularly arginine, is another stimulus of growth hormone secretion (Knopf et al. 1965). Arginine infusion induces an increase in plasma insulin but the blood glucose levels are not influenced. This indicates a collaboration of insulin and growth hormone in the incorporation of amino-acids into protein, a further physiological activity of growth hormone. The first evidence for the effect of growth hormone on protein synthesis in man were shown by Bech *et al. (1957)*. Growth hormone seems to stimulate the transfer of amino-acids from the extracellular to the intracellular compartments (Knobil and Hotschkiss 1964).

Whether these two actions of growth hormone, the lipolytic and the protein synthesizing, are due to action of the same molecule, the one-factor hypothesis (Raben 1965), or due to the two-factor hypothesis of Levine and Luft (1964) which suggest that the so called growth hormone of the anterior pituitary is composed *of two components*, one somatotrophic *with* the protein synthesizing effect and one adipokinetic *with the* lipolytic effect, is yet to be proved. According to the hypothesis of Levine and Luft the immunoassay of HGH will measure both effects.

Supporting the two-factor hypothesis are the results of Trygstad (1967) which have been discussed in Part I page 32

These fundamental functions of growth hormone can explain most of the results of the insulin loads in this study The new environment is energy-consuming and blood sugar decreases during the first 24 hours (Cornblath et al 1961) Person and Gentz (1966) have shown that there is an increase in FFA from rather low levels in cord blood to very high levels within the first 48 hours of life. The high levels remain during the neonatal period. When blood glucose is depressed by insulin growth hormone, by its lipolytic action might be the main regulator to energy homeostasis and consequently increases dramatically When feeding has started the demand for energy from FFA is less important which would explain the more moderate HGH levels at the age of 5—6 days.

However there is no difference in per cent maximal increment between the first and the second period investigated so the lower levels as well could be the result of a successive adaptation to a lower level of growth hormone with increasing maturity of the infant. This also could be an explanation for the results obtained in premature infants their higher degree of immaturity resulting in a slower adaption However for premature infants another factor might be of importance. Blood glucose levels during the neonatal period are lower for prematures compared to full term infants (von Euler et al 1964) The main reason for this would be the markedly lower stores of glycogen until the 37th week of gestation (Shelley and Neligan 1966) The energy demand has to be supplied from other sources, the elevated growth hormone levels raise the FFA levels. For the present weight group Melichar et al. (1964) have shown moderately elevated levels of FFA

As for infants of diabetic mothers they have decreased blood glucose levels during the neonatal period (Pedersen et al 1954) the reason for this being a rapid disposal of glucose from the blood due to hyperinsulinism (Baird and Farquhar 1962) The FFA in infants of diabetic mothers are lower when compared to those in normal infants (Chen et al 1965 and Laron et al 1967) which might be the effect of the functional hyperinsulinism and/or the low HGH values. The most likely explanation for most of the metabolic abnormalities in the infant of diabetic mothers is the maternal hyperglycaemia (Pedersen et al 1954) The better the control of the diabetes of the mother the lower the body weight and fewer symtoms of altered metabolism in the child (Pedersen 1967) A possible hypothesis is that the variations in blood glucose during gestation will increase the demands on the regulatory system The latter might improve and be more mature. Therefore the resting levels would be closer to those found in older infants. Exhaustion of the pituitary or regulary system because of large demands during foetal life would give beside a low basic level a depressed response to hypoglycaemia, which has not been shown.

More difficult to explain is the paradoxical increase in growth hormone after induced hyperglycaemia. Cornblath et al. (1965) have shown that this effect remains about 14 days in full term infants and they have suggested different manners for hypo- and hyperglycaemia to trigger the secretion of growth hormone, and that the pathway for suppression requires time after birth to mature. In all groups of patients in this study (full term infants infants of diabetic mothers and prematures) an increase in growth hormone is induced by hyperglycaemia, most pronounced in prematures. This could fit the hypothesis of Cornblath et al. (1965) Another but more venturous possibility is that in newborn infants even a transient hyperglycaemia is a signal for protein synthesis. Growth hormone is necessary for that and protein synthesis and growth are never as intense as in the neonatal period. A support for this hypothesis would be the significantly greater increase in HGH levels induced by glucose load for prematures

at the age of 5—6 days when compared to the first day of life.

If one accepts the two-factor hypothesis of Levine and Luft (1964) there is another possibility. During insulin load the adipokinetic component is produced in high levels to provoke lipolysis. When glucose increases during glucose load the protein synthesizing somatotrophic component increases. It would be of great interest to repeat the estimations with an immunoassay-system for the two components described by Trygstad (1967).

Stress is another factor proved to increase growth hormone levels (Greenwood and Landon 1966). The stress of labor resulting in elevated levels of 17-OH corticosteroids (Migeon et al. 1956) affects neither the basic levels of growth hormone nor the release of growth hormone by insulin load since there are no differences between the infants delivered by caesarean section and those delivered spontaneously. However the experiment *per se* with the catheterization of the umbilical vein, the moderate lowering of the body temperature and the infusion within 1 minute of a volume which for the glucose load constitutes about 10 % of the blood volume, are stressing factors that might stimulate HGH secretion.

At this time too little is known about factors concerning the neonatal metabolism to give an entire explanation about the fundamental role of growth hormone during this period.

Summary

Growth hormone levels during insulin and glucose load have been studied in normal infants, infants of diabetic mothers and in premature infants during the first week of life.

Base levels of HGH were elevated in all patients when compared to older infants. The highest levels were present on the first day of life. Lower levels were found in infants of diabetic mothers than in the other patients studied.

Insulin-induced hypoglycaemia increased HGH levels in all patients. The increase was more pronounced at the age of one day as compared to 5—6 days if the absolute levels were compared. The increase was more moderate in infants of diabetic mothers. If the response to hypoglycaemia is expressed as the per cent maximal increment from basic levels no difference in response can be shown between the first day of life and the age of 5—6 days or between normal infants and infants of diabetic mothers. For premature infants the response in per cent increment was more pronounced at the end of the first week and of much higher degree than for other infants studied.

Hyperglycaemia induced an increase in HGH levels comparable to that found during hypoglycaemia. The differences between the groups studied are the same as for hypoglycaemia.

Supporting the two-factor hypothesis are the results of Trygstad (1967) which have been discussed in Part I page 32

These fundamental functions of growth hormone can explain most of the results of the insulin loads in this study The new environ ment is energy-consuming and blood sugar decreases during the first 24 hours (Corn blath et al 1961) Person and Gentz (1966) have shown that there is an increase in FFA from rather low levels in cord blood to very high levels within the first 48 hours of life. The high levels *remain during the neonatal* period. When blood glucose is depressed by insulin, growth hormone by its lipolytic action might be the main regulator to energy homeostasis and consequently increases dra matically When feeding has started the demand for energy from FFA is less important which would explain the more moderate HGH levels at the age of 5—6 days.

However there is no difference in per cent maximal increment between the first and the second period investigated, so the lower levels as well could be the result of a successive adaptation to a lower level of growth hor mone with increasing maturity of the infant. This also could be an explanation for the results obtained in premature infants, their higher degree of immaturity resulting in a slower adaption. However for premature in fants another factor might be of importance. Blood glucose levels during the neonatal period are lower for prematures compared to full term infants (von Euler et al 1964) The main reason for this would be the markedly lower stores of glycogen until the 37th week of gestation (Shelley and Neligan 1966) The energy demand has to be supplied from other sources, the elevated growth hor mone levels raise the FFA levels. For the present weight group Melichar et al. (1964) have shown moderately elevated levels of FFA.

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I wish to express my sincere thanks to

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Professor Carl Gemzell, Head of the Department of Gynecology and Obstetrics, who introduced me to the interesting subject human growth hormone, and for his valuable support and advice during the course of the investigation.

Ass. Professor Jan Thorell who introduced me to the immunoassay technique and for stimulating discussion and criticism.

Ass. Professor Paul Roos for the preparation of HGH used in the investigation.

Ass. Professor Sven Kraepelin for his help in selecting most of the patients in the investigation of corticosteroid treated children.

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The preparation of growth hormone used for treatment of the patients has been supported by the Swedish Medical Research Council.

General Summary

PART I

Methodological studies

A radioimmuno-chromatographic assay for human growth hormone (HGH) is described The method has been carefully tested with special reference to the influence of degradation damage of HGH and to the method's applicability to neonatal plasma Recovery experiments have been performed and the precision and sensitivity of the method is comparable with other radioimmunoassays for HGH. The method has been tested clinically and the results are comparable with those obtained by similar methods.

The radioimmuno-chromatorographic technique can be used for the detection of antibodies to HGH.

PART II

Clinical studies

1 The HGH release to insulin induced hypoglycaemia has been studied in 16 normal children and the normal response has been defined as an increase in HGH levels of 10 ng/ml or more.

2 The HGH release in children of short stature has been studied in order to diagnose hypopituitary dwarfism. The HGH release in ten children with proved hypopituitarism was subnormal as defined above Two of fifteen patients without pituitary deficiency showed subnormal response. Five children with Turner's syndrome and two with chondrodystrophic nanism showed a normal HGH response. The HGH response to the insulin tolerance test has been compared with other available tests for the evaluation of pituitary function.

3 Nine hypopituitary dwarfs have been treated with human growth hormone The height increment during the first year of treatment varied between 6 and 16 cm with a mean of 10 5 cm During the second year of treatment the mean was 9 2 cm. No patient became resistant to the treatment and regular tests for the presence of antibodies to HGH were not able to reveal any

4 Seventeen children with long term treatment with corticosteroids for bronchial asthma were investigated for HGH release to insulin induced hypoglycaemia. The response was found to be decreased when compared to normal children and a correlation coefficient of —0 66 was found between dose of corticosteroids and HGH increment.

5 Thirty newborn infants were investigated during the first day of life and at the age of 5—6 days Normal infants, infants of diabetic mothers and premature infants showed elevated fasting levels and a vigorous increase in HGH levels during hypoglycaemia as well as during hyperglycaemia The increase was more pronounced during the first day of life and more moderate in infants of diabetic mothers There was no difference in per cent increment from base levels between normal infants and infants of diabetic mothers. For premature infants the per cent increment was greater compared to the other two groups and was most pronounced at the end of the first week of life. The results are discussed with references to fat and carbohydrate metabolism during the first week of life.

Acknowledgements

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BY GÜNTER KOCH

ALMQVIST & WIKSELLS BOKTRYCKERI AB UPPSALA

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UMEÅ 1968

*From the Departments of Clinical Physiology and Pediatrics,
University of Umeå, and the Department of Pediatrics Karolinska Hospital
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INTRODUCTION

Successful transition from intra- to extrauterine life is dependent on the readjustment of a great number of functions to be accomplished more or less urgently during and following delivery. Among these adaptative processes the most dramatic changes are those occurring in the circulatory and respiratory system. The readjustment processes occurring in these two systems are intimately linked together and interdependent.

In the fetus gas exchange is exclusively achieved with the maternal circulation by means of the placenta. The lungs do not contain any gas. However the alveoli are all open to some degree (Potter 1953 Plank 1967) and appear at term to be equally expanded with liquid (Plank, 1967). This liquid differs in pH, total osmolality total CO_2 protein, sugar urea and electrolyte concentration from amniotic fluid (Adams et al., 1963 a Adams et al. 1963 b). These differences and persisting liquid formation despite artificially induced tracheal obstruction (Carmel et al., 1965) suggest that it may be an ultrafiltrate of blood, with selective reabsorption or secretion by the lung (Adams et al., 1963 b). There is an open communication between the alveoli and the surrounding amniotic fluid (Potter 1953). Intrauterine respiratory movements may occur (cf. Smith 1959) but do not seem to be a regular event. As gestation proceeds, they become rarer and the stimuli producing them are less effective.

Blood flow through the lungs is low. In the sheep fetus at term only about 12 per cent of the total cardiac output goes to the lungs (Dawes 1958). Marked fluctuations due to changes in vasomotor tone and probably related to among other factors blood gas composition, may however occur (Dawes and Mott, 1962 Cook et al., 1963).

The low pulmonary perfusion is due to high vascular resistance in the pulmonary circulation in relation to the resistance in the systemic placental circulation and most of the blood in the pulmonary trunk is deflected through the ductus arteriosus into the descending aorta. In the fetal lamb at term more than 50 per cent of the total aortic flow comes directly from the right ventricle and passes through the ductus arteriosus (Dawes et al., 1953). The left atrium mainly receives blood directly from the inferior vena cava through the foramen ovale. Thus the blood by passes the high-resistance pulmonary circuit, and both ventricles work in parallel behaving as a functionally single ejection system pumping blood into the low resistance systemic placental circulation (Lind and Wegelius, 1954 Lind 1965). In the lamb more than 50 per cent of the combined output is directed to the placenta (Dawes 1958).

When the placental circulation is eliminated at birth the inactive fetal lungs have to take over the function of the placenta as an effective gas exchanger to ascertain sur

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When the placental circulation is eliminated at birth the inactive fetal lungs have to take over the function of the placenta as an effective gas exchanger to ascertain sur-

MATERIAL

Since the purpose of the present investigation was to analyse normal neonatal respiratory function, the subjects of the different studies are fullterm infants who were selected at random. With but a few exceptions the infants had a spontaneous vertex delivery and were normal as regards pregnancy gestational age, labour birth weight, onset of respiration and clinical course during the neonatal period. The cord was in general clamped after cessation of visible pulsations. However case No. 71 (I) had a somewhat delayed first breath, No. 78 (I) a birthweight of only 2360 g. Study II and III include some otherwise healthy prematures with a birth weight between 1290 and 2180 g. Two cases required earlier clamping because the cord was ruptured during the delivery (II) or was twisted around the neck (VI)

No analgesia was used during labour in the first series of studies (I II III) however a chloroform anaesthesia of very short duration was given at the end of the delivery and some of the mothers received intermittent nitrous oxide during contractions during the latter part of labour In the second group of infants (IV V VI) most mothers received nitrous oxide or trichlorethylene or both by inhalation of short duration at the end of the delivery

A total of 172 infants were studied.

vival in the new enviroment. This requires

1) the more or less immediate expansion and aeration of the lungs and opening up of the pulmonary circulation

2) the continued ventilation of the opened alveoli and establishment of an adequate perfusion of the pulmonary vascular bed

3) the adjustment of distribution of alveolar ventilation and perfusion to each other and establishment of sufficient capacity for diffusion of the respiratory gases through the alveolar-capillary membrane.

The transition to extrauterine life thus implies the establishment of a new autonomic function — that of pulmonary respiration, and important changes in the distribution of cardiac output.

The present series of studies was performed to elucidate some of the mechanisms involved in this establishment and to evaluate the efficiency of lung function in the healthy fullterm newborn infant. It is mainly a study of mechanics of breathing aeration of the lungs in terms of functional residual capacity pulmonary ventilation and diffusion, efficiency of gas exchange in terms of arterial blood gases and alveolar arterial oxygen tension gradients and acid base balance Emphasis is laid on development of function. Since available reports of neonatal lungfunction studies are mainly focused on the first minutes and hours of extrauterline life the present studies have been extended to include the entire first week of life.

Respiratory problems present the major threats to survival of the newborn infant (Driscoll and Smith, 1962) They are overwhelmingly the consequence of the infant's failure to complete successfully the respiratory and circulatory adaptation from intra to extrauterine life. Knowledge of the physiological conditions underlying the normal neonatal respiration and its adjustment is a prerequisite for evaluation of the failing mechanisms and for all rational therapeutic measures. Thus all studies aiming at increasing our knowledge of the respiratory and circulatory adjustment have had and continue to have direct practical clinical implications It was under this conception that the reported studies were commenced and conducted.

The need for miniaturization of methods and apparatus and the complete lack of cooperation of the subject to be studied are serious problems to be overcome in pulmonary function investigation in the neonatal period therefore methodological details and reproducibility of methods have been emphasized.

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A total of 172 infants were studied.

METHODS*)

This survey gives only an enumeration of the methods used For a more detailed description the reader is referred to the original papers

MECHANICS OF BREATHING AND PULMONARY VENTILATION (I, II, III)

Tidal volume (V_T) and respiratory rate (f) were determined by means of a »reverse» body plethysmograph, connected to the infant by a face mask (III Karlberg, Cherry Escardó and Koch 1960) The volume changes were recorded by means of an inductive pressure transducer amplifier unit (Elema Schönander) on an ECG direct recorder (Mingograph 42) Flow rate (V) was derived from the volume curve by means of a specially designed electronic device (Karlberg, Cherry Escardó and Koch 1960)

Intraoesophageal pressure was recorded by means of a liquid filled polyethylene catheter 1 mm inside diameter with several holes near the tip over another pressure transducer amplifier unit on a third channel of the Mingograph

FUNCTIONAL RESIDUAL CAPACITY (FRC) (III)

The FRC was determined by means of the closed-circuit method with helium as test gas A nasal coupling was used for connecting the infant to the breathing system.

STEADY STATE PULMONARY VENTILATION AND DIFFUSING CAPACITY (VI)

The breathing circuit used was built according to the box balloon principle and consisted mainly of a glas box serving as a »reverse» plethysmograph enclosing the inspiratory and expiratory bag The respiratory pressure variations were recorded on a Mingograph 42 as described above

A low resistance gravity independent breathing valve was developed. The dead space was 0 8 and ca. 1 7 ml when used in connection with a nasal coupling and a face mask respectively

The *pulmonary diffusing capacity* was determined with the steady state carbon monoxide method (Filley et al 1954) as modified by Linderholm (1957) and calculated from the equation

$$D_{LCO} = \dot{V}_{CO} / (P_{ACO} - P_{\bar{c}CO}) \quad (1)$$

The *pulse rate* was calculated from the simultaneously recorded ECG

Effect of the investigation procedure on the infants basal state No significant changes either in respiratory or in heart rate were induced by application of the breathing mask Pa_{CO_2} ($p < 0.001$) and standard bicarbonate ($p < 0.05$) were however slightly higher and pH ($p < 0.001$) and Pa_{O_2} ($p > 0.05$) slightly lower during than before the sampling procedure During the sampling

*) Symbols used are those suggested in report in Fed Proc. 9 602, (1950)

period itself respiratory and heart rate were virtually unchanged.

The *reproducibility* of the most important data measured and calculated in connection with the determination of DLCO, when examinations at 24 hours and 7 days respectively are considered as duplicate determinations, were in the same order as in resting adults (Table IV)

VENOUS ADMIXTURE (V VI)

Venous admixture (Qs/Q) was calculated from the classical shunt formula after due transformations with the assumption of an unchanged arterial mixed venous oxygen difference of 3.5 ml/100 ml blood during both air and 100 per cent oxygen breathing and during the period of observation.

1) *Total venous admixture or physiologic shunt* (including both anatomic shunt and venous admixture from alveoli with low ventilation/perfusion ratio was estimated during air breathing from the formula

$$\frac{Qs}{Q}\ (\text{air}) = \left[1 + \frac{3.5}{O_2\text{cap}\ (S_{C}O_2 - S_aO_2) + 0.0031\ (P_{A}O_2 - P_aO_2)}\right]^{-1} 100\ (\text{per cent}) \quad (2)$$

where 0 0031 is the amount of oxygen physically dissolved in 100 ml blood per mm Hg (V VI)

2) *Venous admixture due to anatomic right-to-left shunt* was estimated during breathing of pure oxygen after washing-out of nitrogen. Oxygen breathing was performed during 20 minutes in a specially constructed plexiglass hood approximately fitting the infant s head.

Provided arterial $PO_2 > 150$ mm Hg, at which tension hemoglobin may be considered completely saturated the equation used was

$$\frac{Qs}{Q}\ (\text{oxygen}) = \left[1 + 1129/(P_{A}O_2 - P_aO_2)\right]^{-1} 100\ (\text{per cent}) \quad (3)$$

When P_aO_2 was below 150 mm Hg equation (3) was not considered to be valid and the following equation was used

$$\frac{Qs}{Q}\ (\text{oxygen}) = \left[1 + \frac{3.5}{O_2\text{cap}\ (1 - S_aO_2) + 0.0031\ (P_{A}O_2 - P_aO_2)}\right]^{-1} 100\ (\text{per cent}) \quad (4)$$

A nomogram for the PO_2 ranges above and below 150 mm Hg permitting easy estimation of anatomic shunt (Qs/Q) from arterial oxygen tension during breathing of 100 per cent oxygen is given in Fig. 1

Cardiac output (Q) (VI) was estimated from the actually measured oxygen consumption (VO_2) and the assumed value of 3.5 ml/100 ml blood for the arterial – mixed venous oxygen difference using Fick s formula

$$Q = (VO_2/3.5)\quad 100\ (ml) \quad (5)$$

BLOOD COLLECTION (IV V VI)

Since capillary blood is not a reliable substitute for arterial blood during the neonatal period particularly with respect to PO_2 (Koch and Wendel 1967 a) arterial blood had to be collected. In order to avoid disturbance of steady state conditions blood sampling had to be performed by means of an indwelling arterial catheter

Arterial blood was sampled from the descending aorta by means of a polyvinyl ca

METHODS*)

This survey gives only an enumeration of the methods used For a more detailed description the reader is referred to the original papers

MECHANICS OF BREATHING AND PULMONARY VENTILATION (I, II, III)

Tidal volume (V_T) and *respiratory rate* (*f*) were determined by means of a »reverse body plethysmograph, connected to the infant by a face mask (III Karlberg, Cherry Escardó and Koch, 1960) The volume changes were recorded by means of an inductive pressure transducer amplifier unit (Elema Schonander) on an ECG direct recorder (Mingograph 42) Flow rate ($\dot{V}$) was derived from the volume curve by means of a specially designed electronic device (Karlberg, Cherry Escardó and Koch 1960)

Intraoesophageal pressure was recorded by means of a liquid filled polyethylene catheter 1 mm inside diameter with several holes near the tip over another pressure transducer amplifier unit on a third channel of the Mingograph.

FUNCTIONAL RESIDUAL CAPACITY (FRC) (III)

The FRC was determined by means of the closed-circuit method with helium as test gas A nasal coupling was used for connecting the infant to the breathing system.

STEADY STATE PULMONARY VENTILATION AND DIFFUSING CAPACITY (VI)

The breathing circuit used was built according to the box balloon principle and consisted mainly of a glas box serving as a »reverse» plethysmograph enclosing the inspiratory and expiratory bag The respiratory pressure variations were recorded on a Mingograph 42 as described above

A low resistance gravity independent breathing valve was developed. The dead space was 0 8 and ca. 1 7 ml when used in connection with a nasal coupling and a face mask respectively

The *pulmonary diffusing capacity* was determined with the steady state carbon monoxide method (Filley et al 1954) as modified by Linderholm (1957) and calculated from the equation

$$D_{LCO} = \dot{V}_{CO} / (\bar{P}_{ACO} - \bar{P}_{cCO}) \quad (1)$$

The *pulse rate* was calculated from the simultaneously recorded ECG

Effect of the investigation procedure on the infants basal state No significant changes either in respiratory or in heart rate were induced by application of the breathing mask Pa_{CO_2} ($p < 0 001$) and standard bicarbonate ($p < 0 05$) were, however slightly higher and *pH* ($p < 0 001$) and Pa_{O_2} ($p > 0 05$) slightly lower during than before the sampling procedure During the sampling

*) Symbols used are those suggested in report in Fed. Proc. 9 602, (1950)

period itself respiratory and heart rate were virtually unchanged.

The *reproducibility* of the most important data measured and calculated in connection with the determination of D_{LCO} when examinations at 24 hours and 7 days respectively are considered as duplicate determinations were in the same order as in resting adults (Table IV)

VENOUS ADMIXTURE (V VI)

Venous admixture (Q_s/Q) was calculated from the classical shunt formula after due transformations with the assumption of an unchanged arterial – mixed venous oxygen difference of 3.5 ml/100 ml blood during both air and 100 per cent oxygen breathing and during the period of observation.

1) *Total venous admixture or physiologic shunt* (including both anatomic shunt and venous admixture from alveoli with low ventilation/perfusion ratio was estimated during air breathing from the formula

$$\frac{Q_s}{Q}\ (\text{air}) = \left[1 + \frac{3.5}{O_2\text{cap}\ (S_{c}\,O_2 - S_aO_2) + 0.0031\ (P_{AO_2} - P_{aO_2})}\right]^{-1} 100\ (\text{per cent}) \quad (2)$$

where 0 0031 is the amount of oxygen physically dissolved in 100 ml blood per mm Hg (V VI)

2) *Venous admixture due to anatomic right-to-left shunt* was estimated during breathing of pure oxygen after washing-out of nitrogen. Oxygen breathing was performed during 20 minutes in a specially constructed plexiglass hood approximately fitting the infant s head.

Provided arterial $P_{O_2} > 150$ mm Hg, at which tension hemoglobin may be considered completely saturated, the equation used was

$$\frac{Q_s}{Q}\ (\text{oxygen}) = \left[1 + 1129/(P_{AO_2} - P\ O_2)\right]^{1} 100\ (\text{per cent}) \quad (3)$$

When $P\ O_2$ was below 150 mm Hg equation (3) was not considered to be valid and the following equation was used

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A nomogram for the P_{O_2} ranges above and below 150 mm Hg permitting easy estimation of anatomic shunt (Q_s/Q) from arterial oxygen tension during breathing of 100 per cent oxygen is given in Fig. 1

Cardiac output (Q) (VI) was estimated from the actually measured oxygen consumption (V_{O_2}) and the assumed value of 3.5 ml/100 ml blood for the arterial – mixed venous oxygen difference using Fick's formula

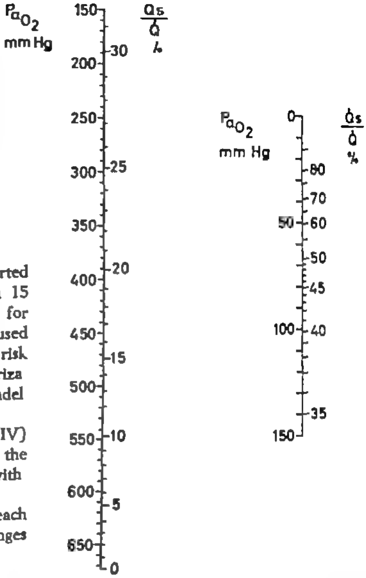
$$Q = (V_{O_2}/3.5)\quad 100\ (\text{ml}) \quad (5)$$

BLOOD COLLECTION (IV V VI)

Since capillary blood is not a reliable substitute for arterial blood during the neonatal period particularly with respect to P_{O_2} (Koch and Wendel, 1967 a) arterial blood had to be collected. In order to avoid disturbance of steady state conditions blood sampling had to be performed by means of an indwelling arterial catheter

Arterial blood was sampled from the descending aorta by means of a polyvinyl ca

FIG 1 Nomogram for calculating anatomic shunt ($\dot{Q}s/\dot{Q}$) from arterial oxygen tension (P_{aO_2}) during 100 per cent oxygen breathing
Left side nomogram for oxygen tensions above 150 mmHg right side nomogram for oxygen tensions below 150 mmHg (Nomograms are based on the assumptions of $P_{AO_2} = 673$ mmHg, arterio-venous O_2 difference = 3.5 ml/100 ml, O_2 cap = 23 ml/100 ml) (V)



theter (feeding tube French size 5) inserted in one of the umbilical arteries within 15 minutes after delivery and left in place for maximally 7 days With the technique used this procedure was considered free of risk and no complications caused by the catherization were observed (Koch and Wendel 1967 b)

Whenever cord blood was sampled (IV) the umbilical artery and subsequently the umbilical vein were directly punctured without clamping the cord

Blood samples between 1 and 5 ml each were collected in 5 ml heparinized syringes and immediately iced.

BLOOD ANALYSES (IV V VI)

Blood gas analyses and determination of pH were performed within 60 minutes after sampling, Pa_{O_2} and Pa_{CO_2} after oxygen breathing were determined immediately

pH was measured at 37 C with a thermostated microglass electrode The same standard phosphate buffer solution (Koch 1965) was used throughout the study

Carbon dioxide tension (Pa_{CO_2}) was determined with a Severinghaus type electrode (Severinghaus and Bradley 1959) and *oxygen tension* (Pa_{O_2}) with a Clark type microelectrode (Clark, 1956) with a polypropylene membrane During a part of the studies (VI) carbon dioxide tension was also measured by the microequilibration technique (Siggaard Andersen et al. 1960)

Standard bicarbonate and *total CO_2 content* were determined by the microequilibration technique or by use of the Siggaard Andersen s alignment nomogram (1963) The validity of this nomogram for neonatal blood was shown by determining the first dissociation coefficient of carbonic acid in umbilical venous blood, and comparing total CO_2 content determined directly by the manometric Van Slyke technique with the values obtained from the alignment nomogram (IV)

Oxygen saturation (S_{O_2}) and *hemoglobin concentration* (Hb) were measured spectro-

photometrically the *hematocrit* (Hct) was determined by microcapillary technique Oxygen *capacity* (O_2 cap) was derived from hemoglobin concentration assuming 1 g hemoglobin to combine with 1.34 ml O_2 STPD (IV)

Lactic acid concentration was determined *enzymatically* (IV) and *pyruvic acid* concentration by the method of Friedeman and Haugen (1943) as modified by Huckabee (1956)

Carbon monoxide content (VI) of arterial blood was determined in 0 1 ml samples by microtechnique (Linderholm, 1965)

GAS ANALYSES (VI)

Fractions of *oxygen carbon dioxide* and *nitrogen* in inspiratory and exspiratory gases were determined according to Scholander (1957) *Carbon monoxide* in the gas phase was measured with a hopcalite CO-meter (Linderholm and Sjöstrand 1956)

For the most important analytical procedures used in this series of studies methodological errors expressed as the standard error of a single determination (Sx) and the coefficient of variation (v) calculated from duplicate determinations are given in Table I

TABLE I.

Reproducibility of some analytical methods estimated from duplicate determinations (IV V VI)

Variable	Dimensions	Method	n	$\bar{x}$	$\bar{d}$	Sx	
pH	units	microelectrode[1]	80	7.327	0 0002	0 0022	
P_{aCO_2}	mm Hg	microelectrode[2]	[illegible]	35.9	0 06	0 6	1 6
P_{O_2}	mm Hg	microelectrode[2]	84	60 6	0 1	0 7	1.2
S_{aO_2}	per cent	spectrophotom.	50	[illegible]1 4	0.3	1.3	1 6
Hb	g/100 ml	spectrophotom.	44	15 05	0 016	0 1	0 7
Hct	per cent	micromethod	50	50 9	0 13	0.3	0 6
Lactic acid	meq/l	enzymatic	50	2 4	0 02	0 12	5 1
Pyruvic acid	meq/l		30	0 14	0 0013	0 003	2 18
C_{CO}	vol. per cent	micromethod	44	0 57	4 6×10-3	1.3×10-2	2.3
F_{CO}	vol per cent	hopcalite[3]	44	4.7×10 2	1.2×10	5 6×10-4	1.2
			[illegible]	9 7×10 2	1.8×10-	9 1×10	0 9
F_{O_2}	vol per cent	Scholander	44	20 81	3 8×10 2	1.9×10 2	9 6×10 2
			44	16 91	3 1×10 3	2.3×10 2	0 13
F_{CO_2}	vol. per cent	Scholander	44	3.11	7 ×10 3	1 9×10 3	0 64

= number of duplicate determinations
x = mean value
d = mean difference between duplicat determinations
Sx = standard error of single determination
= coefficient of variation, per cent

) Radiometer
[2]) Instrumentation Laboratory
[3]) Beckman D
) Eppendorf
[5]) Stålex

RESULTS

THE ONSET OF BREATHING IN TERMS OF PULMONARY VENTILATION AND MECHANICS OF BREATHING (I)

Changes prior to the first breath

Among 10 cases in whom a record prior to the first breath was obtained in 3 instances inspiratory and in 5 expiratory volume changes amounting to 5—25 ml were recorded in general accompanied by slight changes in intraoesophageal pressure

First breaths

In 10 cases (Case No 71 excluded) where the first breath could be recorded this occurred between [illegible] and 55 seconds counted from the moment when the head was outside the vulva The volume displacement effected by the first breath ranged between 12 and 67 ml the maximal intraoesophageal pressure changes during inspiration ranged between −4 and −70 cm H_2O and during expiration between +5 and +70 cm H_2O The subsequent breaths had in general a similar pressure volume pattern but showed a tendency toward decreased magnitudes in both pressure and volume The total intrathoracic pressure swing during the first breath ranged from 40 to 100 cm H_2O

Residual volume

In 7 of 11 infants the end expiratory level of the first breath was between 4 and 30 ml higher than the inspiratory starting level and was mainly maintained at this higher level during the subsequent breaths This volume shift is consistent with the build up of a residual volume In two cases the end expiratory level was constant in two (Nos 48 and 66) it was by 7 and 9 ml respectively lower than the starting level. In these two infants some »expiratory» volume change had been recorded prior to the first breath which suggests that some volume gain may have occurred before recording was started.

Initial breathing pattern respiratory rate and 20 seconds ventilation

There were mainly 3 patterns of initial respiration 1) regular rhythmic respiration with a relatively high respiratory rate (>25/min) 2) regular periodic breathing and 3) breathing with irregular periodicity Accordingly respiratory rate showed large variations and the initial 20 seconds ventilation ranged between 78 and 790 ml

Mechanical factors

Pressure volume diagrams (respiratory loops) of the first breath and in general even the subsequent breaths had a more or less quadratic form indicating high pulmonary resistance and probably at least in most cases low lung compliance Variations in the magnitude of negative and positive pressures necessary and their relationship to each other were however large According to

TABLE II

Mechanics of breathing. Mean values (M) and standard deviation (SD) obtained at the age periods 2—35 minutes, 1—2.5 hours and 24 hours—7 days and statistical significance level (p) of mean differences (birth weight 3430 ± 400 g) (II)

Age group (range)		2—35 minutes M	SD	range			1—2.5 hours M	SD	range		n	1—8 days M	SD	range
Lung compliance, ml/cm H_2O	20	2 7	0 9	1 0—4 0	$p < 0\ 001$	15	3 9	0 9	3 0—6 4	$p < 0\ 001$	31	5 6	1.8	2 6—11 0
Pulm. resistance cm H_2O/l/sec	20	35	20	14—98	$p > 0\ 1$	15	27	14	7—48	$p > 0\ 5$	28	27	12	7—48
Insp. work, total, g cm	20	245	108	54—400	$p > 0\ 05$	15	183	95	60—400	$p > 0\ 8$	28	190	102	66—490
Insp. work, elastive part, %	20	68	14	39—87	$p > 0.7$	15	66	12	42—79	$p > 0\ 05$	28	60	11	42—81
Mean tidal volume (rebreathing) ml	20	[illegible]	7 4	15—44	$p > 0.3$	15	20	6.7	19—4	$p > 0\ 05$	31	34	8 0	20—48

the magnitude of inspiratory pulmonary resistance two rather distinct groups can be separated one with rather low and the other with higher resistance The group with the lower inspiratory pulmonary resistance appears to have a tendency towards higher compliance

Inspiratory work during the first breaths in relation to tidal volume is significantly higher than during quiet breathing, but of the same order as during crying in newborns at the age of some days

FURTHER DEVELOPMENT OF THE MECHANICAL PROPERTIES OF THE LUNG DURING THE FIRST WEEK OF LIFE (II)

As early as at the age of 2—3 minutes i. e after approximately 40—100 breaths the respiratory loops during quiet breathing are smaller and volume and pressure variations less Lung compliance increases and pulmonary resistance total inspiratory work and the part of inspiratory work done to overcome elastic forces decrease There is a fairly rectilinear relationship between compliance pulmonary resistance inspiratory work/V_T^2 respectively and age when plotted on a double logarithmic scale This means that changes proceed most rapidly in the very beginning of extrauterine life and only insignificant changes occur during the period between 24 hours and 8 days of age In eleven infants studied both at 24 hours and 7 days there were no statistically significant differences between the values obtained at the two ages (V_T D [8 days — 24 hours] = 1 ± 9 ml $p > 0\ 6$) lung compliance D = 0.9 ± 2.8 ml/cm H_2O $p > 0.3$ pulmonary resistance D = —2.6 ± 12 1 cm H_2O/l/sec, $p > 0.5$ total inspiratory work D = —10 4 ± 76 g cm, $p > 0\ 6$ elastive part of inspiratory work D —3.9 ± 13.5 % $p > 0.3$)

Mean values found at different age periods, namely 2—35 minutes 60—150 minutes and

mean value ± standard deviation.

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Mean values found at different age periods, namely 2—35 minutes, 60—150 minutes and

mean value ± standard deviation.

24 hours — 7 days are given in Table II Lung compliance corrected for body size differences was 0 79 ± 0 07 1 15 ± 0.3 and 1 68 ± 0 6 ml/cmH_2O/kg birth weight respectively Only for lung compliance there was a statistically significant difference ($p < 0\,001$) between the means of these three age groups

FUNCTIONAL RESIDUAL CAPACITY (III)

The functional residual capacity shows a gradual increase between the age of 1—2 hours and 24 hours In 6 infants who were followed from 1—2 hours up to 24 hours of life this increase was observed in each case and averaged 14 ± 8 ml (from 91 to 105 ml $p < 0\,01$)

No significant change seems to occur between 24 hours and several days of age. FRC averaged 93 ± 18 5 ml (n = 16 range 69—135 ml) at 24 hours and 82 ± 21 ml (n = 9 range 54—103 ml) at the age 6—12 days without a statistically significant difference ($0\,05 < p < 0\,1$) between the means.

Already during the first day of life, FRC and compliance (C) are highly correlated FRC (ml) = 10 1 C (ml/cm H_2O) + 56 4 (n = 17 SEE (y) = 16 1 r = 0 77 $p < 0\,01$) The specific compliance (compliance/FRC) during the first day of life is 0 042 ± 0 01 (n = 17) thus approaching already during the first day relations seen later in life

BLOOD GASES AND ACID-BASE BALANCE DURING THE FIRST WEEK (IV)

There is hypoxemia hypercapnea and both respiratory and non respiratory (metabolic) acidosis at birth as reflected by umbilical

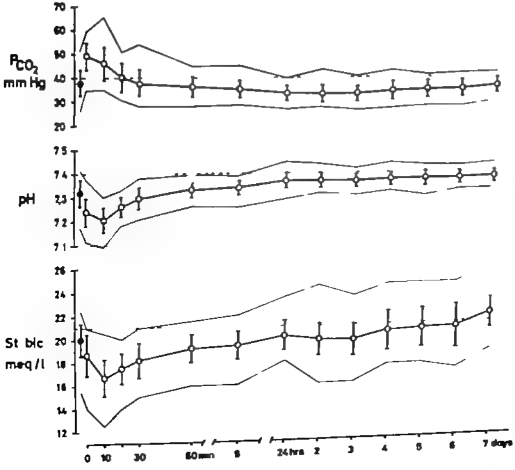

FIG 2. Mean, standard deviation and range of arterial carbon dioxide tension, pH and standard bicarbonate at different ages during the first week of life (IV) Open circles (o) values in blood of th descendi g aorta (at time 0 n umbilical cord ar tery) filled circles ( ) at time 0 values in blood f the umbilical cord vein.

arterial blood (Fig. 2) with accumulation of lactic and pyruvic acid (IV). Acidosis and lactic acid concentration (Fig. 6) further increase during the first minutes following birth, but recede rapidly and steadily during the subsequent minutes and hours. Respiratory acidosis (hypercapnea) is abolished within 30 to 60 minutes after delivery while pH exceeds 7.35 only after 24 hours of life at the same time lactate and pyruvate values have approached adult resting values while P_{CO_2} is about 33 mm Hg. The adjustment of pH to normal adult values thus occurs in spite of persisting hypobasemia which is apparently counterbalanced by hyperventilation. Hypobasemia recedes significantly ($p < 0.001$) during the rest of the first week of life and standard bicarbonate reaches the lower limit of the normal adult range by the 7th day of life. This rise in standard bicarbonate is paralleled by a corresponding increase ($p < 0.001$) in P_{CO_2} from the age of 24—72 hours untill 7 days (IV Fig 2). There are no significant differences in lactic acid concentration between 24 hours and 7 days (1.0 ± 0.15 and 0.9 ± 0.25 meq/l respectively $p > 0.2$, IV).

Normal arterial saturation is on the average achieved by about 5 hours of life by which time P_{aO_2} is about 73 mm Hg without any further significant change during the remainder of the first week of life (Fig. 3).

Oxygen capacity and hematocrit decrease slightly from the age of 5 and 24 hours respectively (Fig 3).

The changes occurring in pH, P_{aCO_2}, standard bicarbonate P_{aO_2} and S_{aO_2} are significantly correlated to age and can be expressed as logarithmic functions of age (Table III) thus permitting prediction of normal values.

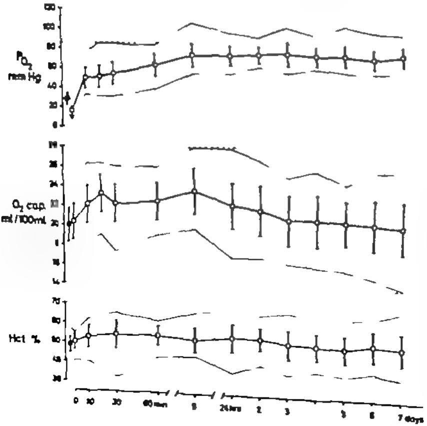

FIG 3 Mean, standard deviation and range of arterial oxygen tension during air breathing, and of oxygen capacity and hematocrit in arterial blood at different ages during the first week of lif (IV). Symbols as in Fig 2.

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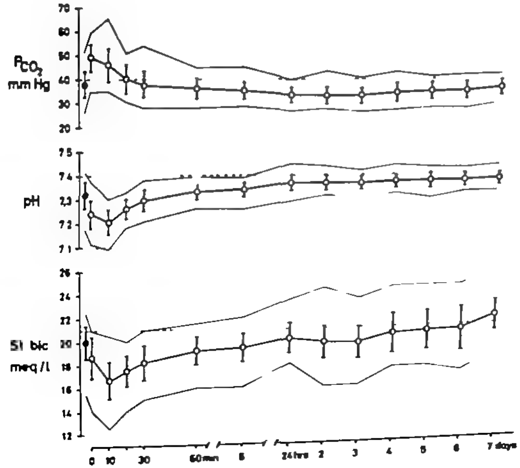

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at the age of 35 minutes averaging 356 mm Hg at the age of 5 hours to 7 days it averaged between 95 and 141 mm Hg.

Venous admixture due to anatomic shunt averaged 24 per cent of right ventricular output at the age of 35 minutes but decreased to an average between 7.6—10.9 per cent during the period 5 hours to 7 days, the lowest values being found at the age of 2 and 3 days (Fig 4)

STEADY STATE PULMONARY VENTILATION AND DIFFUSING CAPACITY (VI)

Obstetrical data and individual data for most of the variables studied in connection with determination of D_{LCO} at 24 hours and 7 days of life are given in the Appendix Tables 1 2, 3 Table IV shows the mean values obtained at 24 hours and 7 days respectively as well as the mean differences.

Minute volume ($\dot{V}_E$) oxygen consumption ($\dot{V}_{O_2}$) carbon dioxide elimination ($\dot{V}_{CO_2}$) and alveolar ventilation ($\dot{V}_A$) are statistically significantly correlated to body size This held also for tidal volume (V_T) when only cases with a regular breathing pattern were selectected (cf VI)

Between 24 hours and 7 days of age there was a slight decrease ($p < 0.01$) of the respiratory rate and the alveolar ventilation equivalent for CO_2 ($\dot{V}_A/\dot{V}_{CO_2}$) and increase ($p < 0.001$) of the respiratory exchange ratio (R) Minute volume ($\dot{V}_E$) decreased and heart rate increased slightly ($p < 0.05$) Changes in tidal volume (V_T) oxygen consumption ($\dot{V}_{O_2}$) ventilation equivalent for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) carbon dioxide elimination ($\dot{V}_{CO_2}$) alveolar ventilation ($\dot{V}_A$) and physiological dead space (V_D) were slight and statistically not significant.

Both the physiological dead space/tidal volume ratio (V_D/V_T) and the diffusing capacity (D_{LCO}) decreased slightly from 24 hours to 7 days ($p < 0.05$)

The ratio V_D/V_T D_{LCO} in relation to $\dot{V}_A$, $\dot{V}_{O_2}$ and body surfac area (BSA) and the alveolar – mean pulmonary capillary oxygen tension difference ($P_{AO_2} - P_{cO_2}$) correspond to standard adult values

A-a O_2 DIFFERENCE AND TOTAL VENOUS ADMIXTURE (VI)

During air breathing Pa_{O_2} was on the average 72 and 74 mm Hg at 24 hours and 7 days of life and the $P_{AO_2} - Pa_{O_2}$ difference 31 and 30 mmHg corresponding to a total venous admixture during air breathing of 20.9 ± 6 and 18.4 ± 5.9 per cent of right ventricular output respectively ($p < 0.05$)

CARDIAC OUTPUT AND OVERALL VENTILATION/PERFUSION RATIO (VI)

Calculated from the assumed value of 3.5 ml/100 ml for the arterial - mixed venous oxygen difference (cf VI) and measured oxygen uptake cardiac output averaged 699 ± 112 ml and 646 ± 101 ml at 24 hours and 7 days respectively This slight change parallels the decrease of $\dot{V}_{O_2}$ from 24 hours to 7 days.

The overall ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) estimated from these values for $\dot{Q}$ and the corresponding measured values for $\dot{V}_A$ averaged 0.63 and 0.66 at 24 hours and 7 days ($0.05 < p < 0.1$)

TABLE III.

Regression equations for pH P_{aCO_2} standard bicarbonate oxygen saturation and P_{O_2} during air breathing, and for P_{O_2} alveolar-arterial oxygen difference and anatomic shunt during oxygen ($F_{IO_2} = 1$) breathing as logarithmic functions of age (independent variable)

Dependent variable	Equation (x = age in hours)	SEE	n	Coefficient of correlation
pH (units)	y = 0.04 × log x + 7.29	0 036	542	0 78*
P_{aCO_2} (mm Hg)	y = — 2.51 × log x + 38.6	4.8	541	—0 49
Stand bic. (meq/l)	y = 1 14 × log x + 18.3	1.6	537	6 02
P_{O_2} (mm Hg)	y = 7 7 × log x + 58.7	10 1	465	0 61**
S_{aO_2} (per cent)	y = 49 2 × log x + 88 8	7 4	192	0.56
P_{O_2} (F_{IO_2} = 1 mm Hg)	y = 81 1 × log x + 407	89	254	0.51
$P_{AO_2} - P_{O_2}$ (F_{IO_2} = 1 mm Hg)	y = —76.9 × log x + 262	84.6	254	—0.51
Qs/Q (F_{IO_2} = 1, %)	y = — 5 1 × log x + 18.8	5 9	254	—0 49 **

SEE = standard error of estimate.
= $p < 0.001$

VENOUS ADMIXTURE DUE TO TRUE ANATOMIC SHUNT DURING THE FIRST WEEK OF LIFE (V)

P_{aO_2} during oxygen breathing averaged 309 mm Hg with a wide range (60—540 mm Hg) at the age of 55 minutes but showed a considerably higher mean level between 527—589 mm Hg, from 5 hours to 7 days of age (Fig 4)

The P_{aO_2} of 60 mmHg was the only value below 100 mmHg observed in this series during oxygen breathing. In spite of this unusually low value the infant appeared normal judging from the clinical condition and from pH, P_{aCO_2} bicarbonate and lactate values. P_{aO_2} during air breathing was 40 mmHg at 60 minutes and 55 mmHg at 5 hours of age at which time P_{aO_2} during oxygen breathing attained 497 mmHg

Correspondingly the average alveolar-arterial oxygen tension difference was highest

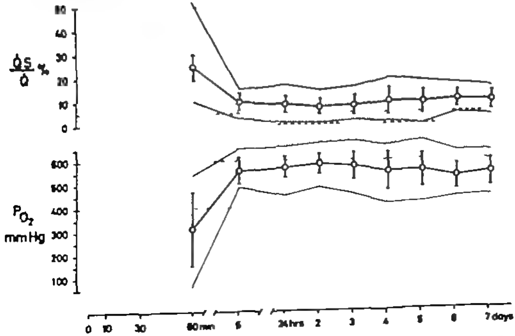

FIG 4 Mean, standard deviation and range of arterial oxygen tension during oxygen breathing and calculated anatomi shunt at different ages during the first week of life (V) Symbols as in Fig. 2

at the age of 55 minutes averaging 356 mm Hg at the age of 5 hours to 7 days it averaged between 95 and 141 mm Hg.

Venous admixture due to anatomic shunt averaged 24 per cent of right ventricular output at the age of 55 minutes but decreased to an average between 7.6—10.9 per cent during the period 5 hours to 7 days the lowest values being found at the age of 2 and 3 days (Fig. 4)

STEADY STATE PULMONARY VENTILATION AND DIFFUSING CAPACITY (VI)

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Stand. bic. (meq/l)	$y = 1.14 \times \log x + 18.3$	1.6	537	6 02
P_{O_2} (mm Hg)	$y = 7.7 \times \log x + 58.7$	10.1	465	0.61
S_{aO_2} (per cent)	$y = 49.2 \times \log x + 88.8$	7.4	192	0.56
P_{aO_2} ($F_{IO_2} = 1$, mm Hg)	$y = 81.1 \times \log x + 407$	89	254	0.51
$P_{AO_2} - P_{O_2}$ ($F_{IO_2} = 1$, mm Hg)	$y = -76.9 \times \log x + 262$	84.6	254	—0.51*
Q_s/Q ($F_{IO_2} = 1$, %)	$y = -5.1 \times \log x + 18.8$	5.9	254	—0.49*

SEE = standard error of estimate.
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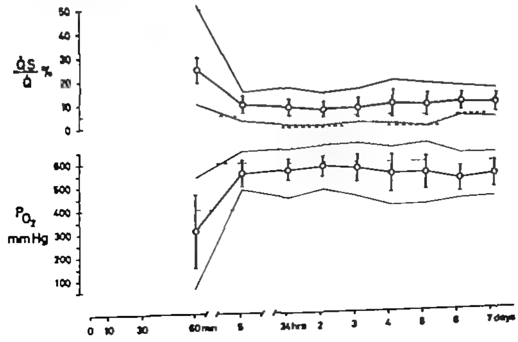

FIG 4 Mean, standard deviation and range of arterial oxygen tension during oxygen breathing and calculated anatomic shunt at different ages during the first week of life (V) Symbols as in Fig 2

	7 days			7 days — 24 hours			
n	M	S D	range	n	D		D %
20	36 5	0 2	36 2 — 36.9	20	0 05	0.8	0.1
[illegible]	123	12	108 —161	24	7	8 7	6
29	39	8	29 — 54	29	— 5	16 0	—11 4
29	632	113	445 —863	29	—52	14 8	— 7 6
29	16 6	2.5	[illegible] — 21 4	29	0 4	14 7	2.5
29	22.6	3.5	15 5 — 29 6	29	— 1 5	16 0	— 6 2
29	28 0	3 2	22.6 — 37 1	29	— 0 5	9 8	— 1.8
29	17 6	2 8	12.3 — 22.4	29	0 7	14.9	4 1
[illegible]	0.78	0 25	0 68— 0.90	29	0 07	7 7	10
29	36 7	3 0	30 1 — 42.3	29	1 8	6 2	5 1
29	425	74	269 —569	29	— 3	13 5	— 0 7
29	18 8	1 8	16 2 — 22 6	29	0 9	10.3	5
29	24 2	2 0	21 4 — 29 1	29	— 1.3	6 3	— 5
29	3.9	1 0	1 7 — 6 4	29	— 0 3	25 3	— 7 1
29	0.24	0 05	0 17— 0.36	29	— 0 03	16 8	—11.5
29	103	3 8	96 —111	29	1	3 9	1
25	2 0	0 5	1 2 — 2.9	23	— 0 2	15.5	— 9
[illegible]	2.5	0 6	1.3 — 3 6	[illegible]	— 0 3	15 5	— 9
[illegible]	10	3	5 — 15	23	0 6	18 8	6.5
29	74	7	62 — 91	29	2	5 0	2 8
29	30	7	11 — 43	29	— 1	16.9	— 3.3
29	18 4	5 9	5 9 — 29 4	29	— 2 6	18 6	—13 3
24	551	61	429 —638	24	—14	3 6	— 2.5
24	122	57.5	50 —252	24	5	24 1	4.3
24	9 7	4 3	4 1 — 18 3	24	0.4	23.1	4.3
[illegible]	58 7	22.1	23 7 — 98 8	[illegible]	15 6	16.3	36
29	646	101	443 —846	29	—43	16 0	— 6 2
29	0 66	0 06	0 57— 0 79	29	0 03	10.3	4.8
29	21 8	1.5	19 5 — 25 0	29	1.8 **	6 0	9 0
29	7 35	0 03	7.30— 7 40	29	0 01		0.1
29	15 4	1 6	12 1 — 18 9	29	— 1 0 **	4 7	— 6.1
27	51 1	7.1	35 8 — 65 8	24	— 4 2	6 6	— 7.6
27	[illegible]	0 2	0 4 — 1 1	26	— 0 2	19.2	—22.2
29	2 5	0 8	1.2 — 4 9	28	— 0 1	23 8	— 3.7

p <0 05
** p <0 01
** p <0 001

v coefficient of variation, per cent

TABLE IV

Means (M) standard deviation (SD) and range of some data obtained for ventilation, intrapulmonary gas exchange and acid-base balance at the age of 24 hours and 7 days and differences (D) between means (VI).

		24 hours		
	n	M	SD	range
Temperature and heart rate				
Rectal temp C	23	36.5	0.4	35.5 — 37.2
Heart rate	27	117	10	88 — 137
Ventilation				
Resp rate	33	44	9	27 — 79
$\dot{V}_E$ ml BTPS	33	703	120	388 — 975
V_T ml BTPS	33	16.5	3.1	10.0 — 22.7
$\dot{V}_{O_2}$ ml STPD	33	24.5	3.9	13.9 — 34.7
$\dot{V}_E/\dot{V}_{O_2}$	33	28.9	3.2	21.9 — 36.9
$\dot{V}_{CO_2}$ ml STPD	33	17.3	2.7	10.0 — 22.8
R	33	0.71	0.05	0.60 — 0.83
P_{CO_2} mm Hg	33	34.7	2.9	29.8 — 41.0
$\dot{V}_A$ ml BTPS	33	442	73	243 — 580
$\dot{V}_A/\dot{V}_{O_2}$	33	18.2	2.2	13.3 — 22.9
$\dot{V}_A/\dot{V}_{CO_2}$	33	25.6	2.4	21.7 — 30.3
V_D, ml BTPS	33	4.3	1.3	2.5 — 7.5
V_D/V_T	33	0.26	0.05	0.17 — 0.38
Diffusion				
$\bar{P}_{A_{O_2}}$ mm Hg	33	103	5.5	89 — 114
$D_{L_{CO}}$ ml/min/mm Hg	26	2.2	0.5	1.2 — 3.1
$D_{L_{O_2}}$ ml/min/mm Hg	26	2.7	0.6	1.5 — 3.8
$\bar{P}_{A_{O_2}} - \bar{P}_{c_{O_2}}$, mm Hg	26	9.4	2.6	4 — 15
Venous admixture				
P_{O_2} mm Hg (air)	33	72	7	62 — 91
$\bar{P}_{A_{O_2}} - P_{O_2}$, mm Hg (air)	33	31	9	11 — 46
Qs/Q tot. % (air)	33	20.9	6.0	7.9 — 29.2
P_{O_2} mm Hg (100 % O_2)	26	566	51	450 — 665
$\bar{P}_{A_{O_2}} - P_{O_2}$ mm Hg (100 % O_2)	26	117	50	12 — 231
Qs/Q anat., % (100 % O_2)	26	9.3	3.5	3.0 — 17.0
(Qs/Q anat./Qs/Q tot.) 100 %	25	43.3	16.1	2.6 — 79.3
Ventilation/perfusion ratio				
$100 \times \dot{V}_{O_2}/3.5 \approx \dot{Q}$ ml	33	699	112	397 — 991
$\dot{V}_A/\dot{Q}$	33	0.63	0.07	0.5 — 0.8
Acid-base balance etc				
St. bic., meq/l	33	20.2	1.3	17.7 — 23.7
pH	33	7.35	0.02	7.30 — 7.41
Hb, g/100 ml	32	16.3	1.6	12.6 — 18.8
Hct per cent	29	55.6	7.4	36.4 — 67.4
S_{COHb} endogeneous, %	32	0.9	0.3	0.5 — 1.7
S_{COHb} at examination, %	31	2.7	0.7	1.7 — 4.9

	7 days			7 days — 4 hours			
	M	SD	range	n	D		D %
20	36 5	0 2	38 2 — 36.9	20	0 05	0.8	0.1
24	123	12	108 —161	24	7	8 7	6
29	39	8	29 — 54	29	— 5	16 0	—11 4
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29	16 6	[illegible]	9 6 — 21 4	29	0 4	14 7	2 5
[illegible]	22 6	3.5	15.5 — 29 6	29	— 1 5	16 0	— 6 2
[illegible]	28 0	3 2	22 6 — 37 1	29	— 0 5	9 8	— 1.8
29	17.6	2.8	12.3 — 22.4	29	0 7	14.9	4 1
29	0 78	0 25	0 68— 0 90	29	0 07	7 7	10
29	36 7	3 0	30 1 — 42.3	29	1 8	6.2	5 1
29	425	74	269 —509	29	— 3	13 5	— 0 7
29	18 8	1 8	16 2 — 22 6	29	0 9	10.3	5
29	24 2	2.0	21 4 — 29 1	29	— 1 3	6 3	— 5
29	3 9	1 0	1 7 — 6 4	29	— 0 3	25 3	— 7 1
29	0 24	0 05	0.17— 0 36	29	— 0 03	16 8	—11.5
29	103	3 8	96 —111	29	1	3 9	1
25	2 0	0.5	1 2 — 2 9	[illegible]	— 0 2	15 5	— 9
25	2.5	0 6	1 5 — 3 6	23	— 0.3	15 5	— 9
[illegible]	10	3	5 — 15	23	0 6	18 8	6.5
29	74	7	62 — 91	29	2	5 0	2.8
29	30	7	11 — 43	29	— 1	16 9	— 3 3
29	18 4	5 9	5 9 — 29 4	29	— 2 6	18 6	—13 3
24	55 1	67	429 —638	24	—14	5 6	— 2.5
24	122	57 5	90 —252	24	5	24.1	4 3
24	9 7	4 3	4 1 — 18 3	24	0 4	23.1	4.3
23	58 7	22.1	23.7 — 98 8	23	15 6 **	16 3	36
29	646	101	443 —846	29	—43	16 0	— 6 2
[illegible]	0 66	0 06	0 57— 0.79	29	0 03	10.3	4 8
[illegible]	21 8	1.5	19 5 — 25 0	29	1 8 **	6 0	9 0
29	7 35	0 03	7.30— 7 40	29	0 01		0.1
29	15 4	1 6	12 1 — 18 9	29	— 1.0	4.7	— 6.1
27	51 1	7 1	35 8 — 65.8	24	— 4 2	6 6	— 7.6
27	[illegible]	0.2	0 4 — 1 1	26	— 0 2	19 2	—22 2
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* $P < 0.05$
** $P < 0.01$
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DISCUSSION

METHODS

The small size and the lack of cooperation of the subject to be studied make pulmonary function investigation in the newborn period difficult and limit its possibilities The present series of studies as well as those of others (Cook et al 1955 Stahlman 1957 Nelson et al 1962 Strang and McGrath 1962 Prod'hom et al 1964 and others) however have demonstrated that suitable methods can be developed or adapted permitting investigation of the main mechanisms in respiratory function even in the youngest age group

If in the present study (VI) in spite of the biological changes occurring, the serial examinations at 24 hours and 7 days of age (Table IV) are considered as duplicate determinations then it appears that for most of the variables of particular importance for respiratory gas exchange including alveolar ventilation and pulmonary diffusing capacity a methodological reliability of the same order as in corresponding investigations in resting adults can be achieved

ONSET OF RESPIRATION AND INITIAL RESPIRATORY ADJUSTMENT

Since at initiation of extrauterine life the fetus emerges from a watery environment into air removal of lung liquid filling the alveolar spaces and upper airways is a prerequisite for successful aeration and gas exchange. In the mature fetal lamb the liquid contained in the lungs at term is in the order of 40—80 ml which appears to be similar to that of the functional residual capacity of gas after initiation of breathing (Howatt et al. 1965) Similar figures ought to apply to the human fetus the functional residual capacity has actually been shown to be of the same magnitude (III Strang and McGrath 1962 Prod'hom et al 1964 Chu et al 1964) Provided there is low surface tension in the lung after introduction of air the resting position of the lungs should thus be the same wether they contain liquid or air (Strang, 1967) Lung liquid can be drained probably mostly from the upper airways, in considerable amounts during the delivery process particularly during vaginal vertex delivery (Karlberg et al. 1962) leading to a more or less extensive air filling of the upper air passages prior to the first breath (III Lind et al 1964) Although water in the alveolar spaces themselves may be absorbed mainly into the pulmonary circulation (Potter 1953) there is at least in the newborn lamb also evidence for removal of lung liquid through lymphatic channels in the pulmonary interstitial tissue (Boston et al 1965) According to Strang (1967) the increase in lymph flow above the fetal level in the first two hours of ventilation could account for the removal of 30 per cent of the water and all the protein in the lung liquid.

The establishment of air liquid interfaces during the first breath generates surface ten

sions the magnitude of which determines further aeration. The high negatives pressures and high lung resistances regularly encountered during the first and often even the following breaths (I) reflect probably mainly cohesive surface tensions According to Laplace's law surface tensions must be expected to diminish with increasing diameter of the air bubble in the alveoli partly filled with air and partly with liquid, i.e. with progressive removal of liquid and its replacement by air It actually seems that the air filled part of the alveolus takes the shape of an optimally-curved spherical bubble (Plank, 1967) Characteristically in most of the infants in which the first breath showed a residual volume the subsequent inspirations proceeded more easily judging from the slope of the inspiratory pressure volume curve

During deflation, surface tension can be expected to exert a retractive pressure and can thus not account for the high positive pressures observed during expiration and the resulting square form of the respiratory loop. These are probably due to upper airway obstruction during the expiratory phase secondary to pharyngo-laryngeal closure (I)

With respect to the inspiratory part similar pressure volume curves as those obtained during the first breath and sometimes the following breaths have been observed in fetal lungs of the lamb when inflated with positive pressure (Strang, 1967) While the pressure magnitude and the slope of the inflation loop does not seem to differ significantly between mature and immature fetal lungs, during deflation, the latter retains less air at decreasing inflating pressures than the former and tends towards loosing all air when pressure returns to zero A similar displacement of the deflation curve towards decreased volume has been found in lung preparations from infants succumbing to the Idiopathic Respiratory Distress Syndrome (IRDS) when compared with the lungs of newborn infants dieing from other than pulmonary causes and was correlated to differences in the surface activity of lung extracts (Gribetz et al 1959 Gruenwald et al., 1962) The low air-retaining capacity of the immature in relation to the mature lamb lung has also been ascribed to surface activity differences namely higher surface tension in the alveoli of the immature lung. By generating higher lung retractive forces high surface tension would not only prompt alveolar collapse but might even tend to suck back liquid into the alveolus (Boston et al. 1965 Strang, 1967)

In accordance with these observations in mature fetal lamb lungs in most of the infants in whom the first breaths could be recorded a residual volume was established during the first or more seldom, during one of the following breaths as shown from a smaller deflation in relation to inflation volume In some cases however such a residual volume was not observed this could signify 1) that replacement of lung liquid by air occurs at a slower rate or 2) that normal liquid replacement persists after expiration but the resting position of the lungs changes tending to diminish thoracic volume or 3) that some aeration has occurred before the first breaths. Cineradiological examination of the onset of respiration (III) shows in agreement with the different types of initation of respiration as shown by the analysis of the volume pressure relationship (I) that initial aeration can proceed more or less easily and rapidly but complete disappearance of air from the lung fields after the first expiration was not observed. While aeration of the upper airways may occur prior to the first breath (III Lind et al. 1964) there is no evidence that significant aeration of alveolar spaces may occur at this stage

While it thus appears that even in the normal infant variation in the mechanical properties at birth is large no definite conclusions as to the causes of this variation can be drawn from the present study (I) It is tempting to speculate that there may

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Since at initiation of extrauterine life the fetus emerges from a watery environment into air removal of lung liquid filling the alveolar spaces and upper airways is a pre-requisite for successful aeration and gas ex change. In the mature fetal lamb the liquid contained in the lungs at term is in the order of 40—80 ml which appears to be similar to that of the functional residual capacity of gas after initiation of breathing (Howatt et al 1965) Similar figures ought to apply to the human fetus the functional residual capacity has actually been shown to be of the same magnitude (III Strang and McGrath 1962 Prod'hom et al. 1964 Chu et al 1964) Provided there is low surface tension in the lung after introduction of air the resting position of the lungs should thus be the same wether they contain liquid or air (Strang, 1967) Lung liquid can be drain ed probably mostly from the upper airways in considerable amounts during the delivery process particularly during vaginal vertex delivery (Karlberg et al. 1962) leading to a more or less extensive air filling of the upper air passages prior to the first breath (III Lind et al 1964) Although water in the alveolar spaces themselves may be ab-sorbed mainly into the pulmonary circulation (Potter 1953) there is at least in the newborn lamb, also evidence for removal of lung liquid through lymphatic channels in the pulmonary interstitial tissue (Boston et al 1965) Ac cording to Strang (1967) the increase in lymph flow above the fetal level in the first two hours of ventilation could account for the removal of 30 per cent of the water and all the protein in the lung liquid.

The establishment of air liquid interfaces during the first breath generates surface ten

sions, the magnitude of which determines further aeration. The high negative pressures and high lung resistances regularly encountered during the first and often even the following breaths (I) reflect probably mainly cohesive surface tensions. According to Laplace's law surface tensions must be expected to diminish with increasing diameter of the air bubble in the alveoli partly filled with air and partly with liquid, i.e. with progressive removal of liquid and its replacement by air. It actually seems that the air filled part of the alveolus takes the shape of an optimally-curved spherical bubble (Plank, 1967). Characteristically in most of the infants in which the first breath showed a residual volume the subsequent inspirations proceeded more easily judging from the slope of the inspiratory pressure volume curve.

During deflation, surface tension can be expected to exert a retractive pressure and can thus not account for the high positive pressures observed during expiration and the resulting square form of the respiratory loop. These are probably due to upper airway obstruction during the expiratory phase secondary to pharyngo-laryngeal closure (I).

With respect to the inspiratory part similar pressure volume curves as those obtained during the first breath and sometimes the following breaths have been observed in fetal lungs of the lamb when inflated with positive pressure (Strang, 1967). While the pressure magnitude and the slope of the inflation loop does not seem to differ significantly between mature and immature fetal lungs during deflation, the latter retains less air at decreasing inflating pressures than the former and tends towards loosing all air when pressure returns to zero. A similar displacement of the deflation curve towards decreased volume has been found in lung preparations from infants succumbing to the Idiopathic Respiratory Distress Syndrome (IRDS) when compared with the lungs of newborn infants dieing from other than pulmonary causes and was correlated to differences in the surface activity of lung extracts (Gribetz et al., 1959 Gruenwald et al., 1962). The low air-retaining capacity of the immature in relation to the mature lamb lung has also been ascribed to surface activity differences, namely higher surface tension in the alveoli of the immature lung. By generating higher lung retractive forces high surface tension would not only prompt alveolar collapse but might even tend to suck back liquid into the alveolus (Boston et al., 1965 Strang, 1967).

In accordance with these observations in mature fetal lamb lungs in most of the infants in whom the first breaths could be recorded, a residual volume was established during the first or more seldom, during one of the following breaths as shown from a smaller deflation in relation to inflation volume. In some cases however such a residual volume was not observed this could signify 1) that replacement of lung liquid by air occurs at a slower rate or 2) that normal liquid replacement persists after expiration but the resting position of the lungs changes tending to diminish thoracic volume or 3) that some aeration has occurred before the first breaths. Cineradiological examination of the onset of respiration (III) shows in agreement with the different types of initation of respiration as shown by the analysis of the volume pressure relationship (I) that initial aeration can proceed more or less easily and rapidly but complete disappearance of air from the lung fields after the first expiration was not observed. While aeration of the upper airways may occur prior to the first breath (III, Lind et al. 1964) there is no evidence that significant aeration of alveolar spaces may occur at this stage.

While it thus appears that even in the normal infant variation in the mechanical properties at birth is large no definite conclusions as to the causes of this variation can be drawn from the present study (I). It is tempting to speculate that there may

be interindividual differences in lipoproteine surface activity and thus in surface tension even among normal term infants

The great interindividual variability with respect to breathing pattern respiratory rate and minute volume as well as to the mechanical properties persists during the first minutes already at 3—10 minutes however a striking similarity of the respiratory loops approaching the pattern seen after some hours and days of life (II) demonstrates the rapidity with which lung structures accomodate for aeration.

As reflected by arterial blood gases (P_{aO_2} P_{aCO_2}) the degree of alveolar aeration and of mechanical adjustment allows very rapidly for effective pulmonary ventilation and gas exchange At 5 to 10 minutes after delivery P_{aCO_2} has already decreased to 46 ± 7 mm Hg and P_{aO_2} in the descending aorta has reached 50 ± 10 mm Hg Analysis focused on the very first minutes of postnatal development have shown that from about one to two minutes adjustment is effective enough to allow for increasing oxygenation and CO_2 elimination as judged from arterial blood gases (Engstrom et al 1966)

By 30—60 minutes of age lung function appears to be firmly established as judged from functional residual capacity mechanical properties of the lung and gas exchange as revealed by arterial blood gases Respiratory acidosis is on the average abolished at this time ($P_{aCO_2} = 38 \pm 6$ mm Hg at 30 minutes and 36 ± 4 mm Hg at 60 minutes of life) while a relative hypoxemia both in terms of oxygen saturation of the hemoglobin and oxygen tension in descending aortic blood persists The relatively low P_{aO_2} compared to normal adult standards at this age has been shown to correspond to an increased alveolar arterial P_{O_2} difference (Prod'hom et al 1964) The low P_{aO_2} in spite of rather normal effective alveolar oxygen tension (P_{AO_2}) at this age appears to be for the most part due to anatomic R L shunt, which probably occurs mainly through normal fetal pathways (foramen ovale and ductus arteriosus) and to a minor degree to ventilation/perfusion inequality i e low ventilation/perfusion ratio According to Prod'hom et al (1964) roughly 2/3 of total venous admixture is due to anatomic shunt at the age of about 90 minutes Estimations based on own figures of P_{aO_2} in the descending aorta during air and oxygen breathing (V) suggest a similar figure namely about 80 per cent of total venous admixture to be caused by anatomic shunt at the age of 55 minutes

FURTHER DEVELOPMENT OF PULMONARY MECHANICS AND LUNG VOLUME

Within a few minutes after delivery respiratory loops during quiet breathing have approached the shape seen later during the neonatal period. At this age (range 2—35 minutes) lung compliance is 2.7 ± 0.9 ml/cm H_2O and increases to 3.9 ± 0.9 ml/cm H_2O at 1—2.5 hours and 5.6 ± 1.8 ml/cm H_2O at the age of 1—8 days (Table II) This increase is statistically highly significant. On the other hand, there is no statistically significant difference between the compliance measured at 24 hours and 8 days respectively The compliance values found after some hours of life (II III) are in good agreement with the values obtained by means of an air filled system for measurement of oesophageal pressure (Swyer et al 1960 Chu et al, 1964) and different techniques for measuring volume changes (cf Polgar 1967) The trend of changes in compliance occurring during the first day of life has been confirmed by Drorbaugh et al. (1963) and Chu et al (1964) On the other hand respiratory work is significantly higher than the values reported by Cook et al. (1957) and Swyer et al (1960) This is apparently due to the significantly bigger tidal volumes obtained with the reverse plethysmograph technique following rebreathing Our values concerning

respiratory work are thus not representative for basal standards but rather to be considered as an index for the changes occurring. On the other hand, the elastive part of respiratory work corresponds fairly well with the values reported by the above mentioned authors.

FRC measured at 0.5—2 hours 24 hours and 3—12 days of age fall into the same range of magnitude, and there is no statistically significant difference between FRC values obtained at an age of 24 hours and 6—12 days respectively ($p > 0.1$) If serial measurements in the same individuals between 1—2 hours and 24 hours of age are compared, there is, however a slight, yet statistically significant increase ($p < 0.01$) suggesting that the increase in compliance is parallelled by a similar yet proportionally smaller increase in FRC As later in life, FRC and compliance are highly correlated ($r = 0.77$) and specific compliance at the age 1—24 hours is on the average 0.042 ± 0.01 If however measurements at 1—2 and at 24 hours are treated separately the specific compliance is shown to increase significantly ($p < 0.01$) from 0.036 ± 0.008 to 0.05 ± 0.01 indicating that after the rapid accomodation occurring during the first minutes true changes in the elastic properties of the neonatal lung continue. A similar increase of specific compliance during the first hours of life has been noted by Chu et al. (1964) using the plethysmographic method (DuBois et al., 1956) for determination of FRC but not after 24 hours of life They enumerate the following possible causes for this initial increase (1) alterations in the elastic elements following repeated stretching, (2) loss of fluid from the lung during the first hours of postnatal life (3) changes in the alveolar surface-active lining or (4) increase with age in the number of alveoli participating in respiration. Changes in elastic properties due to loss of interstitial fluid seems so far the most realistic explanation since it is actually based on experimental evidence of decreasing lung weight in relation to body weight during the first 5 hours (Boston et al. 1965)

The compliance/FRC ratio of 0.055 ± 0.01 found by Chu et al. (1964) after 24 hours (1—7 days) agrees well with that found in the present study using the closed-circuit method for determination of FRC at 24 hours of age (III) as well as with adult standards. This suggests a striking similarity in the elastic properties of the mechanically adapted neonatal lung with that of the normal adult.

The FRC values found in the present study (III) are intermediate between those obtained by identical technique in a group of very early (29.3 ± 2.0 ml/kg) and very late (21.6 ± 1.4 ml/kg) clamped infants less than 6 hours of age (Oh et al., 1967) There is a good general agreement between the FRC measured with the He-method (26.5 ± 5.7 ml/kg birth weight III) the plethysmographic technique (29 ± 7.0 ml/kg Klaus et al., 1960 27.8 ml/kg Klaus et al. 1962 33.8 ± 7.3 ml/kg Auld et al., 1963) and the open-circuit nitrogen-washout method (31.3 ± 11.3 ml/kg Nelson et al 1963 a) in infants over 1 hour of age

When measuring lung volume concurrently with the nitrogen washout and the plethysmographic technique in the same individual Nelson et al. (1963 a) found however significantly higher values in 10 out of 22 infants with the plethysmographic method. They concluded, since the N_2 and the He-method measure the ventilated portion of the thoracic gas volume i. e. true FRC and the plethysmographic technique total thoracic gas volume that some healthy infants may have significant amounts of trapped air i. e. airway obstruction. This is a surprising finding in view of the rather even gas *distribution* shown in the newborn infant (Tooley et al. 1960 Strang and McGrath, 1962 Nelson et al., 1962 b)

While lung compliance shows a steady increase during the first 24 hours of life pulmonary resistance appears to be mainly unchanged after the age of 1—2 hours (Table II) averaging 27 cm H_2O/1/sec. At 2—35 minutes of life pulmonary resistance averaged 35 ± 20 cm H_2O/1/sec, the difference between this value and the value found later is however statistically not significant The values obtained after 1—2 hours of life are in good agreement with those obtained at corresponding ages by using pneumotachygraph flow recording (Swyer et al 1960 26 cm H_2O/1/sec Polgar and String, 1966 34 cm H_2O/1/sec) or calculation of flow rate from volume recording by means of a body plethysmograph (Cook et al 1957 29 cm H_2O/1/sec

Recently Polgar and collaborators succeeded in measuring even the subdivisions of pulmonary resistance airway resistance and lung tissue resistance in the newborn infant They determined airway resistance by means of the total body plethysmograph technique (DuBois et al 1956) and lung tissue resistance by the method of Marshall and DuBois (1956) substracting the airway resistance measured plethysmographically from the pulmonary resistance determined by directly plotting the resistive component of intraoesophageal pressure against airflow on an x y oscillograph (Polgar and String, 1966) By substracting total pulmonary resistance measured when breathing through a plastic oral airway of known resistance from the pulmonary resistance measured when breathing through the nose even nasal resistance to breathing could be estimated (Polgar and Kong, 1965) this latter was found to be 12.1 ± 5.5 cm H_2O/1/sec ($n = 5$) or about 42 per cent of the total airway resistance against about 63 per cent in adults However total pulmonary resistance in this series was higher (47.5 cm H_2O/1/sec) than values reported by other investigators When measured concurrently total pulmonary resistance was $34\ 1 \pm 8.9$ cm H_2O/1/sec and oral breathi airway resistance $25\ 4 \pm 6\ 4$ cm H_2O/1/s yielding an average lung tissue resistance $8\ 7 \pm 6$ cm H_2O/1/sec (Polgar and Strin 1966) this corresponds to approximately per cent of mean pulmonary resistance co rected for nasal resistance Though the err involved in this type of study in the newbo infant is larger than in the adult, these resul should indicate that total mean opposing r sistive forces in relation to minute ventilatio are lower in the newborn infant than in th adult (Polgar 1967) This should mainly b due to lower nasal resistance while oral air way resistance is similar and tissue resistanc somewhat higher in the newborn infant.

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After the rapid initial adaptative processe only minor changes occur during the remainder of the first week of life

During the subsequent hours of extrauterine life arterial oxygen saturation and oxygen tension continue to rise attaining by five hours of age 96 ± 3 per cent and 74 ± 1 mm Hg respectively During oxygen breathing, P_{aO_2} rises to 555 ± 56 mm Hg corresponding to an alveolar arterial P_{O_2} difference of 124 ± 54 mm Hg and an anatomic shunt of $9\ 8 \pm 3\ 9$ per cent of cardiac output. As discussed above these changes coincide with an important rise in lung compliance and probably some adjustment in FRC In spite of further small adjustments in the lung s mechanical properties oxygenation of arterial blood does not undergo any further changes of significance and anatomic shunt appears to be mainly unchanged with however a minimum value at 2 days of age ($7\ 6 \pm 3\ 1$ per cent) Thus even after one week s acclimatization to extrauterine existence the lung of the newborn infant has not yet attained the same efficiency for oxy

genation of arterial blood as that of the normal adult.

Theoretically decreased arterial oxygen tension can be caused either by alveolar hypoventilation or by mechanisms increasing the alveolar-arterial oxygen tension difference. Three factors may contribute to the latter (VI): 1) The *diffusion component* which may give rise to a $P_{AO_2} - P_{cO_2}$ difference in the presence of impaired diffusion, but in the normal subject only under conditions of hypoxic ambient air; 2) the *distribution component* including both alveoli receiving an excess of perfusion (low ventilation/perfusion ratio) and those receiving an excess of ventilation (high ventilation/perfusion ratio, i.e. large "alveolar" dead space) and 3) the *shunt component* due to anatomic shunt, i.e. shunting of venous blood into the post pulmonary circulation thus establishing a $P_{cO_2} - P_{aO_2}$ difference.

Alveolar oxygen and carbon dioxide tensions (VI) exclude alveolar hypoventilation at least from the age of 24 hours but similar alveolar gas tensions have been reported already at the age of 4 hours (Prod'hom et al., 1964) and are, at least in the normal infant, probably present even earlier as judged from arterial P_{CO_2} (IV).

In view of the magnitude of D_{LCO} and the low $P_{AO_2} - P_{cO_2}$ difference observed in the present study the diffusion component does not appear to contribute substantially to the $P_{AO_2} - P_{aO_2}$ difference at least during breathing of air and hyperoxic inspiratory gases.

Thus the alveolar-arterial P_{O_2} difference of 31 and 30 mm Hg during air breathing at 24 hours and 7 days, corresponding to a total venous admixture of on the average 20.9 and 18.4 per cent of the cardiac output (D = 2.5, $p < 0.05$) should be due to the effect of shunt and distribution component.

Since anatomic shunt determined during oxygen breathing was found to be 9.3 ± 3.5 and 9.7 ± 4.3 per cent of cardiac output respectively, it should account for approximately 43 and 59 per cent of total venous admixture at the age of 24 hours and 7 days respectively if one assumes that oxygen breathing does not change significantly neither blood flow through shunt channels nor the arterial-mixed venous O_2 difference (cf. V).

These results are conflicting with those from earlier reports (Nelson et al., 1963 b; Prod'hom et al., 1964) concerning mainly slightly premature infants delivered by caesarean section, in which venous admixture at least after 4 hours of age was considered to be mainly due to true anatomic shunt. The main causes for this discrepancy appear to be methodological differences in measuring P_{O_2} in blood with high oxygen tensions and the difference in gestational age of the infants studied and the type of their delivery (V).

As indicated by the low values of physiological dead space, alveolar dead space due to alveoli with high ventilation/perfusion ratio does not appear to be of any critical importance for gas exchange. This is in accordance with the findings of a very small arterial-alveolar P_{CO_2} difference (Nelson et al., 1962 b).

The contribution of the different components to the total alveolar-arterial oxygen tension difference can be shown to correspond to the following gas pressure gradients (Rahn and Farhi, 1962; Rahn and Farhi, 1964): alveolar dead space component to $P_{aCO_2} - P_{ACO_2}$, low ventilation/perfusion component to $P_{aN_2} - P_{AN_2}$ and the anatomic shunt component to approximately $(P_{AO_2} - P_{aO_2}) - (P_{aCO_2} - P_{ACO_2}) - (P_{aN_2} - P_{AN_2}) = P_{cO_2} - P_{aO_2}$ (VI). Although only P_{O_2} differences have been determined in the present investigation (VI), these differences have been calculated from the mean values obtained at 24 hours and 7 days of age and have been collected in Fig. 5, and opposed to typical figures for normal adults in order to demonstrate the peculiarity of gas exchange in the newborn infant.

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The contribution of the different components to the total alveolar arterial oxygen tension difference can be shown to correspond to the following gas pressure gradients (Rahn and Farhi 1962 Rahn and Farhi 1964) alveolar dead space component to $P_{CO_2} - P_{ACO_2}$ low ventilation/perfusion component to $P_{aN_2} - P_{AN_2}$, and the anatomic shunt component to approximately $(P_{AO_2} - P_{aO_2}) - (P_{CO_2} - P_{ACO_2}) - (P_{aN_2} - P_{AN_2}) = P_{cO_2} - P_{O_2}$ (VI). Although only P_{O_2} differences have been determined in the present investigation (VI) these differences have been calculated from the mean values obtained at 24 hours and 7 days of age and have been collected in *Fig. 5* and opposed to typical figures for normal adults in order to demonstrate the peculiarity of gas exchange in the newborn infant.

While lung compliance shows a steady increase during the first 24 hours of life pulmonary resistance appears to be mainly unchanged after the age of 1—2 hours (Table II) averaging 27 cm H_2O/l/sec. At 2—35 *minutes of life pulmonary resistance* averaged 35 ± 20 cm H_2O/l/sec, the difference between this value and the value found later is however statistically not significant. The values obtained after 1—2 hours of life are in good agreement with those obtained at corresponding ages by using pneumotachygraph flow recording (Swyer et al 1960 26 cm H_2O/l/sec Polgar and String, 1966 34 cm H_2O/l/sec) or calculation of flow rate from volume recording by means of a body plethysmograph (Cook et al 1957 29 cm H_2O/l/sec

Recently Polgar and collaborators succeeded in measuring even the subdivisions of pulmonary resistance airway resistance and lung tissue resistance in the newborn infant. They determined airway resistance by means of the total body plethysmograph technique (DuBois et al. 1956) and lung tissue resistance by the method of Marshall and DuBois (1956) substracting the airway resistance measured plethysmographically from the pulmonary resistance determined by directly plotting the resistive component of intraoesophageal pressure against airflow on an x y oscillograph (Polgar and String, 1966) By substracting total pulmonary resistance measured when breathing through a plastic oral airway of known resistance from the pulmonary resistance measured when breathing through the nose, even nasal resistance to breathing could be estimated (Polgar and Kong 1965) *this latter was found to be* $12 1 \pm 5 5$ cm H_2O/l/sec ($n = 5$) or about 42 per cent of the total airway resistance against about 63 per cent in adults However total pulmonary resistance in this series was higher (47.5 cm H_2O/l/sec) than values reported by other investigators When measured concurrently total pulmonary resistance was $34 1 \pm 8.9$ cm H_2O/l/sec and oral breathing airway resistance $25 4 \pm 6 4$ cm H_2O/l/sec *yielding an average lung tissue resistance* of $8 7 \pm 6$ cm H_2O/l/sec (Polgar and String, 1966) this corresponds to approximately 40 per cent of mean pulmonary resistance corrected for nasal resistance. Though the error involved in this type of study in the newborn infant is larger than in the adult, these results should indicate that total mean opposing resistive forces in relation to minute ventilation are lower in the newborn infant than in the adult (Polgar 1967) This should mainly be due to lower *nasal resistance* while *oral* airway resistance is similar and tissue resistance somewhat higher in the newborn infant.

LATE ADJUSTMENT OF INTRAPULMONARY GAS EXCHANGE

After the rapid initial adaptative processes only minor changes occur during the remainder of the first week of life

During the subsequent hours of extrauterine life, arterial oxygen saturation and oxygen tension continue to rise attaining by five hours of age 96 ± 3 per cent and 74 ± 12 mm Hg respectively During oxygen breathing, P_{aO_2} rises to 555 ± 56 mm Hg corresponding to an alveolar arterial P_{O_2} difference of 124 ± 54 mm Hg and an anatomic shunt of $9 8 \pm 3.9$ per cent of cardiac output As discussed above these changes coincide with an important rise in lung compliance and probably some adjustment in FRC In spite of further small adjustments in the lung s mechanical properties oxygenation of *arterial blood does not undergo* any further changes of significance and anatomic shunt appears to be mainly unchanged, with however a *minimum value at 2 days* of age ($7 6 \pm 3 1$ per cent) Thus even after one week s acclimatization to extrauterine existence the *lung of the newborn infant has* not yet attained the same efficiency for oxy

corresponding values of estimated Q was 0.63 and 0.66 at 24 hours and 7 days respectively and thus significantly lower than in adults. Even these figures suggest the presence of an important number of alveoli with low ventilation/perfusion ratio which has been shown to account for part of the total venous admixture. The slight increase in overall V_A/Q between 24 hours and 7 days, though statistically not significant, is in accordance with the finding of a decreasing contribution of the distribution component to total venous admixture during the same age period.

ACID-BASE BALANCE

Composition of cord blood during delivery reflects the more or less pronounced disturbance of the functional relationship between mother and fetus during labour and delivery (James 1965) but does not reflect the normal basal condition in utero. Great interindividual differences in the degree of this disturbance even in the course of the normal delivery obviously account for the wide variation of normal P_{O_2}, P_{CO_2}, pH and bicarbonate values reported in both arterial and venous cord blood (cf. Wulf 1967, IV).

There are no figures available for human fetal blood gas and acid-base relations in the undisturbed basal state in utero. It is however well established (cf. IV) that there is maternal respiratory alkalosis during pregnancy secondary to hormone induced hyperventilation, compensated by hypobasemia which results in unchanged or slightly elevated pH. Hyperventilation corresponds to a P_{aCO_2} of about 30—32 mm Hg and a decrease of standard bicarbonate by about 3 meq/l while P_{O_2} is within the normal range (IV).

With respect to the structure of the human placenta and its functional properties (Metcalfe 1967, Wulf 1967) it seems reasonable to assume a P_{CO_2} for umbilical venous blood during intrauterine steady state conditions only a few mm Hg higher than the maternal arterial P_{CO_2} since the composition of the intervillous capillary space blood must lie between that of maternal arterial and uterine venous blood and P_{CO_2} is likely to be lower than the 38 mm Hg found in umbilical venous blood at the end of the delivery process (IV).

This value is admittedly somewhat lower than the umbilical venous P_{CO_2} values reported in most of the previous studies (cf. Wulf 1967) but it is in perfect agreement with that found by Engström et al. (1966) which is probably due to the fact that in these two studies analyses were performed shortly after blood sampling.

On the other hand an important P_{O_2} gradient must be expected through the placental barrier because of the oxygen consumption of the placenta itself which must be significant at least near term (Dawes 1965) and veno-arterial shunts which seem to be present on both sides of the barrier (Metcalfe 1967, Wulf 1967). According to Dawes (1965) reasonable figures would be 20 to 30 mm Hg for umbilical arterial and 40 to 50 mm Hg for umbilical venous P_{O_2} which would cover the observations on different species and also the upper limits of the figures reported for human cord blood during or immediately after delivery.

While it thus appears that the fetus in utero is living in a state of slight hypocapnea and decreased oxygen tension according to adult standards and as judged from umbilical venous pH at birth and from resting maternal lactate values (Derom, 1964) if ever only in a slightly acidotic environment, the delivery process induces more or less pronounced respiratory and metabolic acidosis due to CO_2 retention and accumulation of fixed acids along with hypoxemia which increase postnatally until a maximum is reached at about 1—2 minutes (Engström et al. 1966, IV). Subsequent recovery from the acidotic state at birth is primarily achieved by pulmonary elimination of carbon dioxide while recession of true metabolic acidosis as judged from lactate concentrations will take several hours up to one day (IV, Fig. 6). This adjustment

The arterial alveolar P_{N_2} difference cal culated on the basis of shunt estimations is in good agreement with the urinary-alveolar P_{N_2} difference actually determined in the newborn infant (Rahn and Farhi 1964) Since nitrogen is an inert gas its pressure in the urine is equal to that in the tissues and in the arterial and venous blood (cf Rahn and Farhi 1964)

It is noteworthy that the contribution of the low ventilation/perfusion distribution component decreased from about 57 per cent of total venous admixture at 24 hours to about 40 per cent at 7 days ($p < 0.01$) This finding is in perfect agreement with the ob servation of a decreasing urinary alveolar P_{N_2} difference in the newborn infant during the first 5 days of life (Rahn and Farhi 1964)

A further reduction of the distribution component appears to occur during the fol lowing months of life In the infant of some months of age the distribution component has been estimated to account for only about 10 per cent of total venous admixture (Riegel 1967)

Calculation of cardiac output from oxygen uptake and an arterial mixed venous oxygen difference of 3.5 ml/100 ml yields values in surprisingly good agreement with figures ob tained by direct measurement (Gessner et al 1965 Burnard et al 1966 Arcilla et al 1967) The overall pulmonary ventilation perfusion ratio calculated from V_A and the

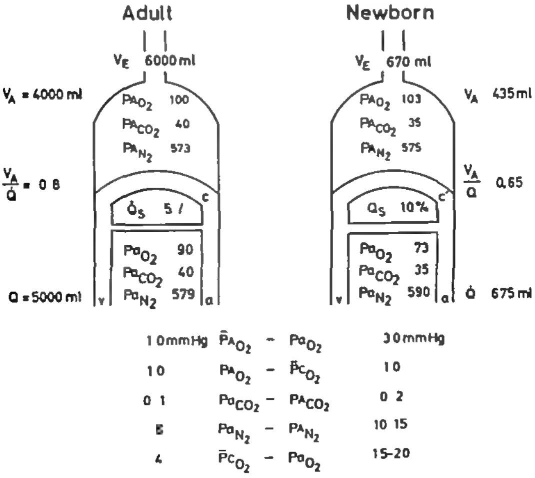

FIG 5 Comparison between typical figures of respiratory exchange in the adult and the newborn infant after the first day of life (VI)

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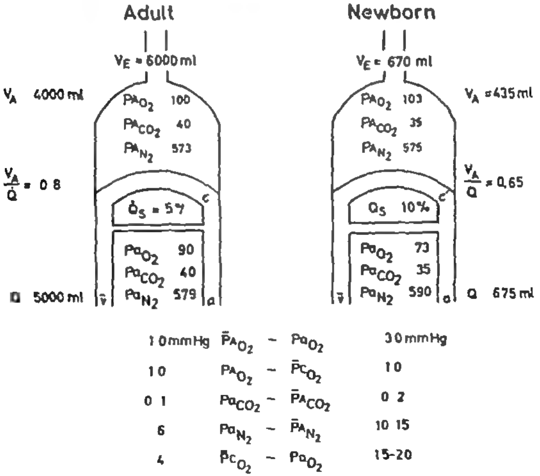

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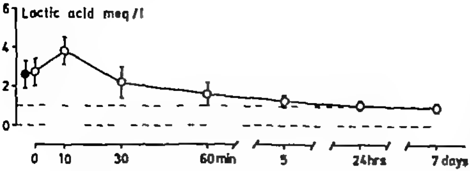


FIG 8 *Mean and standard deviation of arterial lactic acid concentration at different ages during the first week of life (IV) Symbols as in Fig. 2.*

leads at 24 hours of life to a pattern of acid base status very similar to that of the mother prior to labour i.e a hypocapnea corresponding to a P_{aCO_2} of about 33 mm Hg a hypobasemia corresponding to a standard bicarbonate concentration of about 20 meq/l and a bicarbonate ion concentration of about 19 meq/l and with a pH slightly beneath 7 4 During the further course of the first week P_{aCO_2} increases towards normal adult standards paralleled by an increase in bicarbonate concentration with mainly unchanged lactate levels (Fig 6)

The behavior of P_{CO_2} bicarbonate and lactate suggests that in the normal newborn infant after the age of 24 hours there is if any only insignificant »true metabolic acidosis» i e accumulation of fixed acids In accordance with conditions in the pregnant woman it rather appears that after the age of 24 hours hyperventilation is the primary change which is counterbalanced by a secondary hypobasemia. The cause for this hyperventilation in relation to the metabolic rate is not obvious It may be due to a »presetting of the infant's respiratory center to values to which it had probably been exposed in utero or to a sensibilization of the respiratory center by similar mechanisms as those acting in adult man during altitude acclimatization. Carbon dioxide sensitivity curves in the newborn actually show a similar decrease of carbon dioxide stimulation threshold (Avery et al 1963) as in pregnant women and in altitude adapted subjects (Kellogg, 1963) during their altitude sojourn as well as after return to sea level Though subjected to great interindividual variations the main part of reduction of the increased ventilation after return from altitude to sea level appears to occur on the average during the period of approximately one week (cf IV) which agrees quite well with the observed changes in the newborn infant.

There is evidence that the normal P_{aO_2} in resting subjects breathing air at sea level is low enough to constitute a mild ventilatory stimulation, but becomes effective only when the individual is sensitized to lower P_{aCO_2} (Kellogg 1963) Since there is only a weak, yet statistically significant, correlation between P_{aCO_2} and P_{aO_2} during the first week of life it is however improbable that a chemoreceptor drive plays a major role in the origin of neonatal hyperventilation.

SUMMARY

During gestation the placenta subserves the external respiration of the fetus as well as its metabolism. With the initiation of extra-uterine life the placental circulation is eliminated and the fetus emerges from a watery environment into air. This implies the establishment of a new autonomic function, that of pulmonary respiration, which process is intimately linked to a profound readjustment of the circulation.

The present series of investigations has been performed to elucidate certain of the processes involved in pulmonary gas exchange and to evaluate its efficiency compared to adult standards during the period of adjustment to extrauterine life. Though the most important and rapid changes in this adaptative process occur during the first seconds and minutes of extrauterine life they continue far beyond this period. Observations have therefore been extended until the end of the neonatal period defined as the first week of life; this has been considered particularly important as information as to the later period of this adjustment is scarce or lacking. Emphasis is laid on development of function.

Because of the significant morbidity and mortality of the newborn infant in disorders of respiration all investigations throwing more light on the normal respiratory mechanisms and their alterations in disease have important practical implications by improving diagnostic possibilities and facilitating objective evaluation of therapeutic measures.

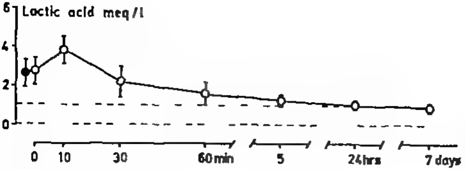
A total of 172 healthy fullterm infants born after an uneventful pregnancy of normal length and uncomplicated vertex delivery are the subjects of the different studies.

The size of the subjects to be studied and the lack of cooperation posed special methodological problems. Suitable procedures and methods permitting reproducible and valid measurements have been developed or adapted for the study of mechanics of breathing, functional residual capacity, pulmonary ventilation, diffusing capacity and gas exchange. Since capillary P_{O_2} does not accurately reflect arterial P_{O_2} a safe procedure permitting arterial blood sampling without disturbing steady state conditions had to be developed.

The onset of respiration and initial aeration of the lungs is characterized by the generation of very high resistive forces, probably mainly due to high surface tension. Subsequently lung compliance increases while lung resistance and inspiratory work decrease, the speed of these changes being highest in the beginning and slowing down subsequently.

Within one hour after delivery the functional residual capacity amounts to 40—80 ml and shows a relation to lung compliance similar to that later in life. Changes after 24 hours of life are insignificant.

There is hypoxemia, CO_2 retention and accumulation of fixed acids, i.e. respiratory and metabolic acidosis at birth. The respira



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tory component of acidosis is on the average abolished at 30 minutes and metabolic acidosis at 24 hours of life P_{CO_2} attains a minimum of about 33 mm Hg at 24 hours of life and increases slightly to 36 mm Hg at 7 days This hyperventilation appears to be counterbalanced by a corresponding hypobasemia which recedes during the subsequent days following closely the increase of P_{CO_2} This regulation shows a striking similarity with the changes occurring during and after adaptation to altitude

Arterial oxygen tension during air breathing increases within 5 hours to on the average about 73 mmHg, after which time no further significant changes occur Arterial oxygen tension is thus significantly lower than in normal adults

Arterial oxygen tension during oxygen breathing averages 309 mmHg at 55 minutes of life and between 527 and 589 mmHg during the period between 5 hours and 7 days of life corresponding to an anatomic R—L shunt of about 24 and between 7 6 and 10 9 per cent of cardic output respectively

Among the different variables studied in connection with the determination of diffusing capacity during steady state conditions at the age of 24 hours and 7 days only the following variables show a statistically significant change during this period heart rate respiratory rate minute ventilation ($\dot{V}_E$) the alveolar ventilation/carbon dioxide elimination ratio (V_A/V_{CO_2}) the respiratory exchange ratio (R) the dead space/tidal volume ratio (V_D/V_T) the pulmonary diffusing capacity for CO the total venous admixture the anatomic shunt/total venous admixtu ratio

Alveolar ventilation in relation to oxyg consumption physiological dead space relation to tidal volume the pulmonary di fusing capacity for CO in relation to oxyge consumption alveolar ventilation and bo surface area and the alveolar – mean pulm nary end capillary oxygen tension differen are of the same order as in healthy restir adults

The alveolar arterial oxygen tension di ference is in the order of 30 mm Hg an mainly unchanged during the age of 24 hou and 7 days It is thus significantly highe than in healthy adults Both anatomic shu and ventilation/perfusion inequality i.e al veoli with low ventilation/perfusion rati account for this difference After the initi adaptation the contribution from ventila tion/perfusion inequality decreases during th first week of life

In accordance with these findings th overall ventilation/perfusion ratio was esti mated to be on the average about 0 65 wit a slight tendency to increase between 2 hours and 7 days

The changes of most of the variables fol lowed continuously from birth to 7 days ca be expressed as a logarithmic function of ag showing that the adaptative changes procee most rapidly in the initial stage

Even at the age of 7 days the lung of th newly born infant has not yet attained th same efficiency with respect to oxygen ex change as that of the healthy adult

RÉSUMÉ

Durant la gestation, le placenta subvient à la respiration du foetus aussi bien qu'à son métabolisme. C'est avec le début de la vie extra-utérine que la circulation placentaire est supprimée et que le foetus surgit à l'air quittant un milieu aqueux. Ceci implique, d'urgence l'établissement d'une nouvelle fonction autonome celle de la respiration pulmonaire Ce processus est intimement lié à une profonde réadaptation de la circulation.

Les présentes séries de recherches ont eu pour but d'éclaircir quelques-uns des processus mis en jeu dans l'échange gazeux pulmonaire et d'évaluer leur efficacité comparée à la norme chez l'adulte durant la période de l'adaptation à la vie extra-utérine. Bien que les changements les plus rapides et les plus importants de cette adaptation se réalisent pendant les premières secondes et minutes de la vie extra-utérine ils se prolongent au-delà de cette période On a donc continué les observations jusqu'à la fin de la période néonatale la première semaine de vie par définition. On a considéré cela comme d'autant plus important que les informations sur la période tardive de l'adaptation sont rares ou inexistantes. Le point a été mis sur le développement de la fonction respiratoire

Le taux tojours considérable de la mortalité néo-natale est en grande partie attribuable aux difficultés de l'adaptation de l'hématose à la naissance. En améliorant les possibilités de diagnostic et d'évaluation des moyens therapeutiques employés au cours des troubles respiratoires les recherches destinées à éclaircir les mécanismes respiratoires physiologiques et leurs deviations patho-physiologiques au cours de détresse respiratoire ont une importance pratique considérable

Un total de 172 enfants venus à terme et en bonne sante après une grossesse sans histoire d'une longueur habituelle et un accouchement à présentation normale sans complications a servi de sujets aux diverses études.

La taille des sujets à étudier et leur manque de coopération ont posé des problèmes de méthodes particuliers Des procédes et des méthodes appropriés permettant des mesures reproductibles et exactes ont été développés ou adaptés à l'étude de la mécanique respiratoire, de la capacité fonctionnelle résiduelle, de la ventilation pulmonaire de la capacité de diffusion et de l'échange gazeux pulmonaire Enfin, on a du étudier la validite du sang capillarie pour remplacer le sang artériel. Le résultat etant négatif en ce qui concerne P_{O_2}, on a du développer un procédé sans danger permettant de prélever du sang artériel sans troubler les conditions stables

Le début de la respiration et l'aération initiale des poumons sont caracterisés par l'apparition de forces de très haute résistance dues surtout probablement, à la haute tension de surface. Ensuite l'accomodation (compliance) pulmonaire augmente tandis que la résistance pulmonaire et le travail

tory component of acidosis is on the average abolished at 30 minutes and metabolic acidosis at 24 hours of life P_{CO_2} attains a minimum of about 33 mm Hg at 24 hours of life and increases slightly to 36 mm Hg at 7 days This hyperventilation appears to be counterbalanced by a corresponding hypobasemia which recedes during the subsequent days following closely the increase of P_{CO_2} This regulation shows a striking similarity with the changes occurring during and after adaptation to altitude

Arterial oxygen tension during air breathing increases within 5 hours to on the average about 73 mmHg after which time no further significant changes occur Arterial oxygen tension is thus significantly lower than in normal adults

Arterial oxygen tension during oxygen breathing averages 309 mmHg at 55 minutes of life and between 527 and 589 mmHg during the period between 5 hours and 7 days of life corresponding to an anatomic R—L shunt of about 24 and between 7 6 and 10 9 per cent of cardic output respectively

Among the different variables studied in connection with the determination of diffusing capacity during steady state conditions at the age of 24 hours and 7 days only the following variables show a statistically significant change during this period heart rate respiratory rate minute ventilation (V_E) the alveolar ventilation/carbon dioxide elimination ratio (V_A/V_{CO_2}) the respiratory exchange ratio (R) the dead space/tidal volume ratio (V_D/V_T) the pulmonary diffusing capacity for CO the total venous admixture the anatomic shunt/total venous admixture ratio

Alveolar ventilation in relation to oxygen consumption physiological dead space in relation to tidal volume the pulmonary diffusing capacity for CO in relation to oxygen consumption alveolar ventilation and body surface area and the alveolar – mean pulmonary end capillary oxygen tension difference are of the same order as in healthy resting adults

The alveolar arterial oxygen tension difference is in the order of 30 mm Hg and mainly unchanged during the age of 24 hours and 7 days It is thus significantly higher than in healthy adults Both anatomic shunt and ventilation/perfusion inequality i e. alveoli with low ventilation/perfusion ratio account for this difference After the initial adaptation, the contribution from ventilation/perfusion inequality decreases during the first week of life

In accordance with these findings the overall ventilation/perfusion ratio was estimated to be on the average about 0 65 with a slight tendency to increase between 24 hours and 7 days

The changes of most of the variables followed continuously from birth to 7 days can be expressed as a logarithmic function of age showing that the adaptative changes proceed most rapidly in the initial stage.

Even at the age of 7 days the lung of the newly born infant has not yet attained the same efficiency with respect to oxygen exchange as that of the healthy adult.

ZUSAMMENFASSUNG

Während der Schwangerschaft besorgt die Placenta den äusseren Gasaustausch und Stoffwechsel des Feten. Mit dem Übergang vom Leben im Wasser d.h. in utero in unsere Luftatmosphäre bei der Geburt entfällt der Placentarkreislauf. Diese Umstellung setzt das unmittelbare Einsetzen einer neuen autonomen Organfunktion voraus, die der Lungen, zum Zwecke des äusseren Gasaustauschs. Dieser Funktionswandel der Lunge ist eng mit tiefgreifenden Umstellungen und Anpassungen des Kreislaufs verbunden.

Ziel der vorliegenden Untersuchungen war es einige der bei der Entwicklung des pulmonalen Gasaustauschs beteiligten Faktoren und Funktionen klarzulegen und ihre Effektivität während der Anpassungsperiode im Vergleich zum gesunden Erwachsenen zu untersuchen. Obwohl die dringlichsten und raschesten Veränderungen im Verlauf dieses Anpassungsvorgangs während der ersten Sekunden und Minuten des extrauterinen Lebens erfolgen, erstrecken Sie sich weit über diesen Zeitabschnitt hinaus. Die vorliegenden Untersuchungen wurden daher auf die gesamte Neonatalperiode d. h. die erste Lebenswoche ausgedehnt. Dies erschien umso wichtiger als unsere Kenntnisse in Bezug auf den späteren Teil der postnatalen Adaptation spärlich sind bzw. entsprechende Untersuchungsresultate gänzlich fehlen. Besonderes Gewicht wurde auf die Veränderungen der Lungenfunktion während der ersten Lebenswoche gelegt.

Der überwiegende Teil der immer noch hohen und während der letzten Jahrzehnte wenig veränderten Neugeborenensterblichkeit beruht auf Schwierigkeiten in der Ausbildung eines adäquaten pulmonalen Gasaustausches. Durch Verbesserung der diagnostischen Möglichkeiten und der Grundlagen zur Beurteilung therapeutischer Massnahmen haben alle Untersuchungen, die zu verbesserter Einsicht in das physiologische und pathophysiologische Geschehen bei der normalen und gestörten Anpassung der Lungenatmung führen, unmittelbare praktische Bedeutung.

Im Ganzen wurden 172 gesunde Kinder untersucht, die nach unauffälliger Schwangerschaft von normaler Dauer und nach unkomplizierter vaginaler Entbindung geboren worden waren. Der klinische Verlauf während der ersten Lebenswoche war bei allen Kindern unauffällig.

Die Grösse der Probanden und das Fehlen jeglicher Möglichkeit zur Mitarbeit in dieser Altersgruppe stellen besondere methodologische Probleme. Brauchbare Verfahren und Methoden mit ausreichender Reproduzierbarkeit und Validität wurden zum Studium von Lungenmechanik, funktioneller Residualkapazität, Lungenventilation, Diffusionskapazität und intrapulmonalem Gasaustausch entwickelt, oder fur die besonderen Verhältnisse modifiziert. Da Kapillärblut kein zuverlässiger Ersatz für arterielles Blut zum Studium der Atemgase insbesondere in Bezug

inspiratoire diminuent la vitesse de ces changements étant tres élevee au début et diminuant ensuite

Une heure après la naissance la capacité fonctionnelle residuelle atteint de 40 à 80 ml et presente un rapport avec la compliance pulmonaire semblable à ce qu il sera plus tard dans la vie. Apres 24 heures les changements sont insignifiants

A la naissance il y a hypoxemie rétention de CO_2 et accumulation d acides fixes c est à-dire acidose respiratoire et métabolique La composante respiratoire d acidose est abolie à 30 minutes en moyenne et l acidose métabolique à 24 heures Le P_{CO_2} atteint un taux minimal d environ 33 mm Hg à 24 heures et augmente legèrement jusqu à 36 mm Hg à 7 jours Cette hyperventilation semble être compensee par une hypobasemie correspondante qui diminue par la suite en suivant de près l augmentation de P_{CO_2} Cette régulation présente une analogie frappante avec les changements survenant durant et apres l adaptation à l altitude

La tension de l oxygène arteriel augmente rapidement jusqu à atteindre la moyenne de 73 mm Hg, à l âge de 5 heures Ensuite aucun autre changement de quelque signification n intervient. Elle est donc significativement plus basse que chez l adulte normal

A l âge de 55 minutes le shunt veino-artériel vrai (anatomique) représente environ 24 % du debit cardiaque De 5 heures jusqu à l âge de 7 jours il varie entre 8 et 11 % Cette reduction survenant au cours des premières heures de la vie correspond vraisemblablement à la forte diminution ou suppression des shunts veino-artériels au niveau des communications foetales

Parmi les différentes variables étudiées lors de la mesure de la capacité de diffusion, sous »steady state à l âge de 24 heures et de 7 jours seules les variables suivantes montrent un changement statistiquement significatif pendant cette période , frequence cardiaque frequence respiratoire, ventilation pulmonaire (V_E) quotient respiratoire (R) rapport entre espace mort et volume courant (V_D/V_T) rapport entre ventilation alvéolaire et élimination de CO_2 ($\dot{V}_A/\dot{V}_{CO_2}$) capacité pulmonaire de diffusion pour CO rapport entre shunt veino-artériel vrai (anatomique) et shunt veino-artériel total (contamination veineuse) (voir Tableau IV)

La ventilation alvéolaire par rapport à la consommation d oxygène $\dot{V}_A/\dot{V}_{O_2}$, ainsi que la capacité pulmonaire de diffusion pour CO par rapport à la consommation d oxygène, et par m² de surface corporelle et le $\bar{P}_{AO_2} - P_{cO_2}$ sont du même ordre que chez l adulte normal au repos

La difference de tension d oxygène alveolo-arteriel ($\bar{P}_{AO_2} - P_{aO_2}$) est de l ordre de 30 mm Hg, et reste à peu près inchangée entre 24 heures et 7 jours Elle est ainsi significativement plus élevée que chez l adulte normal Elle est due à parts approximativement egales à un shunt veino-artériel anatomique et à une inégalité du rapport ventilation/perfusion (contribution venant des alveoles avec rapport ventilation/perfusion diminué) Après l adaptation initiale l importance de la contamination veineuse due à l inégalité ventilation/perfusion par rapport au shunt veino-artériel total diminue pendant la première semaine de vie

En accord avec ces résultats on a évalué le rapport ventilation/perfusion total à 0 65 en moyenne avec une légere tendance à augmenter pendant la période d observation.

Les changements de la plupart des variables suivis d une manière continue de la naissance à 7 jours peuvent être exprimés par des fonctions logarithmiques de l âge montrant que les changements adaptatifs se déroulent le plus rapidement au stade initial

Même à l âge de 7 jours le poumon du nouveau-né n a pas encore atteint la même efficacite quant à l échange d oxygène que celui de l adulte normal.

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Ziel der vorliegenden Untersuchungen war es einige der bei der Entwicklung des pulmonalen Gasaustauschs beteiligten Faktoren und Funktionen klarzulegen und ihre Effektivität während der Anpassungsperiode im Vergleich zum gesunden Erwachsenen zu untersuchen. Obwohl die dringlichsten und raschesten Veränderungen im Verlauf dieses Anpassungsvorgangs während der ersten Sekunden und Minuten des extrauterinen Lebens erfolgen, erstrecken Sie sich weit über diesen Zeitabschnitt hinaus. Die vorliegenden Untersuchungen wurden daher auf die gesamte Neonatalperiode, d. h. die erste Lebenswoche, ausgedehnt. Dies erschien umso wichtiger als unsere Kenntnisse in Bezug auf den späteren Teil der postnatalen Adaptation spärlich sind bzw. entsprechende Untersuchungsresultate gänzlich fehlen. Besonderes Gewicht wurde auf die Veränderungen der Lungenfunktion während der ersten Lebenswoche gelegt.

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auf P_{O_2} ist, musste ein risikofreies Verfahren zur Gewinnung von arteriellem Blut ohne Storung der steady state Bedingungen ent wickelt bzw angepasst werden.

Beim Einsetzen der Atmung und der ini tialen Belüftung der Lunge kommt es zum Auftreten von hohen Widerstandskraften denen wahrscheinlich hauptsachlich hohe Oberflächenspannungen zugrunde liegen Im weiteren Verlauf nimmt die Lungencompli ance zu wahrend der Lungenwiderstand und die inspiratorische Atemarbeit abnehmen Diese Veranderungen erfolgen am schnellsten im Anfang und nehmen allmahlich ab

Innerhalb von 60 Minuten nach der Geburt betragt die funktionelle Residualkapacitat 40—80 ml Die spezifische Lungencompliance (C_L/FRC) steigt wahrend der ersten 24 Stunden und erreicht Werte die mit denen des gesunden Erwachsenen identisch sind

Bei der Geburt hat des Neugeborene eine Hypoxamie CO_2-Retention und Anhäufung fixer Sauren d h eine respiratorische und metabolische Acidose Die respiratorische Komponente ist im Durchschnitt 30 Minuten nach Geburt und die metabolische Acidose im Alter von 24 Stunden ausgeglichen. P_{aCO_2} erreicht im Alter von 24 Stunden mit 33 mm Hg ein Minimum und steigt dann allmählich auf 36 mm Hg am 8 Lebenstag an Diese Hyperventilation scheint durch eine ent sprechende sekundare Hypobasamie kompensiert zu werden die im Lauf der ersten Lebenswoche zurückgeht und dabei eng dem Anstieg des P_{CO_2} folgt. Diese Anpassung zeigt eine auffällige Ahnlichkeit mit den Veranderungen, die während und nach Höhenanpassung beim Erwachsenen beobach tet werden können

Die arterielle Sauerstoffspannung steigt in nerhalb von 5 Stunden auf im Durchsmitt 73 mm Hg an und zeigt danach während der ersten Lebenswoche keine signifikanten Ver änderungen P_{aO_2} ist demnach signifikant niedriger als beim gesunden Erwachsenen.

Die Kurzschlussblutmenge auf Grund von anatomischen Rechts Links-Shunts betragt 55 Minuten nach der Geburt im Durchschnitt ca 24 % des Minutenvolumens sinkt inner halb der ersten 5 Stunden auf knapp 10 % und zeigt wahrend des Restes der ersten Lebenswoche nur geringfugige Veranderungen Ursache der deutlichen Abnahme zwischen 55 Minuten und 5 Stunden durfte das Aufhören oder zumindesten eine deut liche Verminderung von Rechts Links Shunts durch fetale Kreislaufverbindungen (Foramen ovale Ductus arteriosus Botalli) sein.

Von den verschiedenen Variablen die im Zusammenhang mit der Diffusionskapazität der Lungen unter steady state-Bedingungen im Alter von 24 Stunden und 7 Tagen bestimmt wurden zeigen nur die folgenden eine statistisch signifikante Veranderung im Verlauf dieser Periode Herzfrequenz, respiratorischer Quotient (R) und Verhältnis anatomischer Shunt/gesamte venose Kurz schlussdurchblutung einen Anstieg Atemfrequenz, Minutenventilation (V_E) Verhält nis alveoläre Ventilation/CO_2-Ausscheidung (V_A/V_{CO_2}) Verhaltnis physiologischer Tot raum/Atemzugvolumen (V_D/V_T) Diffusionskapazität für CO sowie die gesamte venose Kurzschlussdurchblutung eine Abnahme (siehe Tabelle IV)

Die alveolare Ventilation im Verhaltnis zum Sauerstoffverbrauch (V_A/V_{O_2}) der physiologische Totraum im Verhältnis zum Atemzugvolumen (V_D/V_T) die Diffusions kapazität für CO im Verhältnis zum Sauer stoffverbrauch, zur alveolären Ventilation und zur Körperoberfläche sowie P_{AO_2} — P_{cO_2} sind in derselben Grössenordnung wie beim gesunden Erwachsenen unter Ruhebedingungen

Die alveolo-arterielle Sauerstoffdruckdiffe renz bei Luftatmung liegt in der Grössenord nung von 30 mm Hg und ändert sich kaum vom Ende des ersten Lebenstages bis zum Ende der ersten Woche. Sie ist damit deut lich höher als beim gesunden Erwachsene

Anatomischer Rechts-Links Shunt und venöse Beimischung von Alveolen mit niedrigem Ventilations/Perfusions Verhältnis scheinen in nahezu gleichem Ausmass zu dieser Differenz beizutragen. Der Anteil auf Grund ungleichen Ventilations/Perfusions Verhältnisses nimmt im Lauf der ersten Lebenswoche ab

In Übereinstimmung mit diesen Ergebnissen ergab sich für das Gesamt Ventilations/Perfusions-Verhaltnis ein Durchschnittswert von 0.65 mit einer geringen Steigerungstendenz während der ersten Lebenswoche.

Die Veränderung der meisten der von der Geburt bis zum achten Lebenstag systematisch untersuchten Variabeln kann als logarithmische Funktion des Alters ausgedruckt werden (Tabelle III) Dies zeigt, dass die Anpassungsvorgänge am raschesten im Initialstadium erfolgen.

Selbst im Alter von 7 Tagen hat die Neugeborenenlunge in Hinsicht auf den pulmonalen Sauerstoffaustausch noch nicht die gleiche Effektivität erreicht wie die des Erwachsenen.

auf P_{O_2} ist musste ein risikofreies Verfahren zur Gewinnung von arteriellem Blut ohne Störung der steady state Bedingungen ent wickelt bzw angepasst werden.

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APPENDIX

TABLE 1
Obstetrical Data (VI).

No. sex	Birth-weight (g)	Height (cm)	Age of mother (yrs)	Parity	Gest. age (weeks)	Duration labour (hs)	Anaesthesia Nitrous oxide	Anaesthesia Trichlor ethylene
1 M	3480	52	34	2	42	3.5	+	+
2 F	3290	52	24	1	41	3.7	+	+
3 F	2710	47	18	1	41	16.6	+	+
4 F	3290	52	19	1	39		+	—
5 M	3490	54	25	1	42	7.7	+	+
6 M	4070	53.5	22	1	39		+	+
7 F	4060	52.5	24	2	39		+	+
8 F	3190	47	23	1	41	5.0	+	+
9 M	3650	52.5	21	2	42	1.2	0	0
10 F	3370	50	30	2	39	10.9	+	+
11 F	3540	52	22	2	41		+	+
12 M	4000	54	26	2	41		+	+
13 F	4460	52	25	1	42		—	+
14 F	3000	51.5	28	1	39		+	+
15 F	3190	50	22	1	40	3.3	+	+
16 M	3850	52	27	2	41	2.4	+	+
17 F	3740	51	21	2	40	4.2	+	+
18 F	3120	50.5	25	1	40	2.8	+	+
19 M	3200	50	24	1	39	3.6		
20 F	3630	52	34	3	39	9.5	+	+
21 M	4200	54	26	2	42	4.9	0	0
22 M	4430	51.5	29	2	43	5.2	+	—
23 F	4170	55	24	1	42	5.9	+	+
24 M	3610	53	20	1	41	7.1	+	+
25 M	4280	54	17	1	41	4.2	+	+
26 M	3880	49.5	25	3	41		+	+
27 M	3490	50	35	3	40	2.6	+	+
28 M	3430	50	40	4	40	3.2	+	—
29 F	3830	53	22	1	40	8.1		
30 M	3530	52	26	1	39	7.6	+	+
31 M	3720	51	24	1	40	6.1	+	+
32 F	3180	52	23	2	40			
33 F	2880	49	32	3	41	3.3	+	+
Mean	3604	51.5	25.4	2	40.5	5.5		
SD	436	1.9	5	1	1.1	3.3		

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15	1	109	41	687	17.0	25	27.8	17.7	0.70	439	0.27	35.1	20.0	7.325	15.9	—
	7	161	52	730	14.0	25.2	28.0	19.8	0.79	494	0.21	42.3	21.5	7.331	15.5	59
16	1	110	37	638	17.2	23.0	27.7	15.6	0.68	490	0.20	30.6	21.0	7.346	18.2	0.67
	7	113	31	662	14	22.6	29.2	17.4	0.77	468	0.21	32.5	22.0	7.370	14.2	0.73
17	1	105	36	679	18.8	20.4	33.3	16.9	0.83	468	0.22	3	20.0	7.391	18.1	0.95
	8	130	41	723	17.6	26.4	73	20.4	0.7	471	0.25	30.2	24.0	7.370	16.8	0.81
18	1	122	27	522	19.3	21.1	24.8	15.1	0.72	399	0.22	36.8	18.7	7.304	18.2	0.71
	7	138	38	508	14.1	19.7	25.8	15.1	0 6	349	0.20	37.7	20.8	7.319	17.3	0.62
19	1	111	33	594	10.8	19.9	29.9	15.1	0.76	364	0.23	38.3	19.3	.298	17.6	1.00
	7	125	50	722	14.4	22.5	32.1	17.0	0.76	480	0.32	32.3	19.7	7.317	17.0	0.70
20	1	118	35	794	22.7	23.2	34.2	16.0	0.69	472	0.33	30.0	17.7	7.321	14.1	0.73
	7	108	32	649	20.3	23.5	27.7	16.0	0.68	465	0.20	30.1	20.0	7.341	12.5	0.68
21	1	117	50	794	15.9	26.0	29.6	19.0	0.71	492	0.28	35.6	21.5	7.373	15.5	0.72
22	1	137	44	975	22.1	28.0	34.8	22.4	0.80	580	0.33	33.7	20.2	7.362	—	1.08
23	1	107	41	813	19.8	27.5	29.6	21.1	0.77	579	0.20	32.4	22.9	7.308	17.4	1.18
24	1	120	41	674	16.4	26.9	25.0	19.0	0.71	441	0.24	37.8	20.1	7.350	15.6	1.40
	7	113	31	462	14.9	15.5	29.8	12.3	0.79	269	0.30	39.8	23.2	7.334	15.5	1.04
25	1	112	50	749	15.0	28.0	26.7	17.4	0.62	492	0.23	31.2	19.0	7.311	16.3	1.43
	7	117	31	623	20.1	27.8	22.6	18.9	0.69	499	0.20	33.8	19.5	7.327	15.7	0.93
26	1	130	46	767	16.7	23.1	33.2	17.0	0.74	465	0.29	33.1	19.0	7.338	16.4	1.69
	6	143	34	645	19.0	28.5	22.6	20.5	0.72	462	0.19	38.5	19.5	7.300	17.3	0.90
7	1	119	40	695	17.4	23.2	29.9	16.7	0.72	491	0.20	30.5	19.8	7.352	14.5	1.58
	7	114	33	708	21.4	24.2	29.2	18.9	0.78	453	0.23	36.4	21.5	7.359	14.8	1.02
5	1	124	35	738	21.1	24.8	29.8	18.2	0.74	529	0.20	29.8	18.5	7.340	14.7	1.29
	7	111	36	582	16.2	20.3	28.7	15.4	0.76	423	0.25	31.3	22.1	7.402	14.0	1.12
1	1	120	44	674	15.3	23.9	28	17.2	0.72	416	0.27	36.0	20.0	7.332	17.1	1.06
	6	113	29	531	18.3	20.5	25.9	15.5	0 6	370	0 1	36.6	20.4	7.337	17.0	0.79
	1	88	34	605	17.8	22.5	26.9	14.6	0.66	399	0.25	32.5	20.0	7.367	18.8	1.22
	7	118	29	313	17.7	21.3	24.1	14.7	0.69	373	0.18	34.1	25.0	7.387	14.6	—
	1	116	40	627	15.7	22.4	28.0	15.4	0.69	383	0.28	35.1	23.7	7.412	13.1	0.98
	7	109	30	537	17.9	20.5	26.1	15.4	0.75	340	0.33	39.7	23.0	7.350	13.6	1.07
	1	115	45	630	14.0	22.0	28.6	15.3	0.69	350	0.32	38.6	21.0	7.337	14.2	0.92
		122	44	775	17.6	23.7	32.7	19.5	0.82	420	0.36	40.8	23.3	7.354	12.5	0.96
	1		40	782	19.5	26.0	30.0	17.7	0.68	508	0.26	30.6	20.2	7.392	14.1	0.61

TABLE 2

Heart rate, data for ventilation and acid-base balance, hemoglobin concentration and CO-saturation (VI)

No.	Age days	Heart rate	Resp rate	$\dot{V}_E$ ml BTPS	V_T ml BTPS	$\dot{V}_{O_2}$ ml STPD	$\dot{V}_E/\dot{V}_{O_2}$	$\dot{V}_{CO_2}$ ml STPD	R	$\dot{V}_A$ ml BTPS	V_D/V_T	P_{aCO_2} mm Hg	St. bic. meq/l	pH	Hb g/100 ml	SCOHb per cent
1	1	—	47	859	18.3	32.0	26.9	21.0	0.66	503	0.32	36.5	19.4	7.345	13.8	0.73
	6	—	38	586	15.4	21.0	27.9	16.3	0.78	386	0.23	36.7	24.1	7.373	13.0	0.59
2	1	—	[illegible]	668	17.1	20.6	32.4	16.6	0.80	414	0.28	35.7	21.0	7.330	16.8	0.61
	7	—	52	786	15.1	27.7	28.4	20.6	0.74	496	0.26	37.0	21.0	7.354	15.1	0.43
3	1	—	34	388	11.4	13.9	27.8	10.0	0.72	243	0.22	35.8	19.0	7.339	18.8	0.69
	7	—	30	474	15.8	18.3	25.9	14.0	0.77	335	0.18	36.2	22.4	7.399	16.0	0.40
4	1	—	36	697	19.4	24.3	28.7	18.4	0.76	400	0.34	40.2	23.5	7.374	12.6	0.74
	7	—	33	527	16.0	17.2	30.7	14.0	0.82	336	0.26	36.3	22.2	7.382	12.1	0.57
5	1	—	53	925	17.4	34.7	26.6	22.8	0.66	484	0.38	41.0	20.5	7.335	16.6	0.72
	7	—	32	445	13.9	17.5	25.4	12.9	0.74	303	0.27	37.0	23.0	7.381	17.2	0.51
6	1	118	37	622	16.8	22.4	27.7	17.5	0.78	412	0.24	36.9	19.7	7.340	16.3	0.59
	7	125	34	582	17.1	23.5	24.8	18.6	0.79	403	0.21	40.2	24.0	7.358	15.6	0.69
7	1	122	79	931	11.8	25.2	36.9	17.6	0.70	456	0.36	33.8	20.5	7.372	17.9	0.82
	7	117	54	863	16.0	26.1	33.1	21.6	0.83	569	0.24	33.1	19.5	7.320	17.4	0.59
8	1	124	54	621	11.5	18.7	33.2	11.0	0.59	333	0.31	32.5	20.0	7.351	16.7	0.82
	7	127	44	760	17.3	20.5	37.1	18.5	0.90	462	0.29	34.8	21.2	7.373	14.9	0.86
9	1	116	39	649	16.6	24.4	26.6	17.8	0.73	472	0.17	32.8	21.5	7.360	17.5	0.88
	7	120	38	548	14.4	20.7	26.4	18.3	0.88	443	0.19	36.0	21.5	7.366	15.8	0.62
10	1	109	38	607	16.0	23.9	25.3	17.5	0.73	420	0.20	37.0	20.0	7.345	15.7	0.65
	7	124	44	643	14.6	21.5	30.0	17.9	0.83	419	0.23	37.9	21.0	7.323	14.9	0.77
11	1	122	56	793	14.2	29.7	26.7	21.8	0.73	569	0.19	33.2	19.5	7.350	16.1	0.83
	7	127	40	729	18.2	26.6	27.4	22.4	0.84	524	0.19	37.2	22.0	7.351	14.8	0.81
12	1	101	44	803	18.3	27.8	28.9	19.3	0.70	477	0.31	35.9	20.0	7.307	18.6	0.87
	7	123	50	782	15.6	29.6	26.4	22.1	0.74	478	0.28	40.9	21.5	7.344	16.7	0.89
13	1	125	56	635	11.3	29.0	21.9	17.3	0.60	386	0.24	39.7	19.5	7.313	18.6	0.96
	7	126	[illegible]	740	15.1	24.5	30.2	21.1	0.88	538	0.17	35.2	20.5	7.350	18.9	0.87
14	1	135	52	573	11.0	23.0	24.9	14.9	0.65	352	0.24	37.4	18.5	7.313	17.3	1.18
	7	140	[illegible]	510	9.8	19.4	26.3	15.5	0.80	332	0.18	41.0	23.5	7.320	10.0	0.02

15	1	109	41	60		25.3	27	7	70	439	27	35.1	20	1	1	
	7	161	52	730	14.0	25	29.0	19.9	0.79	494	0.21	2.3	21.5	325 / 331	5 / 1.5	0.59
16	1	110	37	636	17.2	23.0	27.7	15.6	0.68	450	0.20	30.6	21.0	7.346	16.2	0.67
	7	113	31	682	21.4	22.6	29.2	17.4	0.77	468	0.21	32.5	22.0	7.370	14.2	0.73
17	1	105	[illegible]	679	18.8	20.4	33.3	16.9	0.63	468	0.22	32.2	20.0	7.391	18.1	0.95
	6	130	41	723	17.6	26.4	27.3	20.4	0.77	471	0.25	39.2	24.0	7.370	16.8	0.81
18	1	122	27	522	19.3	21.1	24.8	15.1	0.72	359	0.22	36.8	18.7	7.304	18.2	0.71
	7	136	38	508	14.1	19.7	25.8	15.1	0.76	349	0.20	37.7	20.8	7.319	17.3	0.62
19	1	111	[illegible]	594	10.8	19.9	29.9	15.1	0.78	364	0.23	38.3	19.3	7.298	17.6	1.00
	7	125	[illegible]	722	14.4	22.5	32.1	17.0	0.76	460	0.32	32.3	19.7	7.317	17.0	0.70
20	1	118	35	794	22.7	23.2	34.2	16.0	0.69	472	0.33	30.0	17.7	7.321	14.1	0.73
	7	108	32	649	20.3	23.5	27.7	16.0	0.68	465	0.20	30.1	20.0	7.341	12.5	0.68
21	1	117	50	794	15.9	26.8	29.6	19.0	0.71	492	0.28	35.6	21.5	7.373	15.5	0.72
22	1	137	44	975	22.1	28.0	34.8	22.4	0.80	580	0.33	33.7	20.2	7.362	—	1.08
23	1	107	41	813	19.8	27.5	29.6	21.1	0.77	579	0.20	32.4	22.9	7.398	17.4	1.18
24	1	120	41	674	16.4	26.9	25.0	19.0	0.71	441	0.24	37.8	20.1	7.350	15.6	1.40
	7	113	31	462	14.9	15.3	29.8	12.3	0.79	269	0.30	39.8	23.2	7.334	15.5	1.04
25	1	112	50	749	15.0	28.0	28.7	17.4	0.62	492	0.23	31.2	19.0	7.311	16.3	1.41
	7	117	31	623	20.1	27.6	22.6	18.9	0.69	499	0.20	33.8	19.5	7.327	15.7	0.93
26	1	130	46	767	16.7	23.1	33.2	17.0	0.74	465	0.29	33.1	19.0	7.336	16.4	1.69
	6	143	34	645	19.0	28.5	22.6	20.5	0.72	462	0.19	38.5	19.5	7.300	17.3	0.90
27	1	119	40	695	17.4	23.2	29.9	16.7	0.72	491	0.20	30.5	19.8	7.352	14.5	1.58
	7	114	33	706	21.4	24.2	29.2	18.9	0.78	453	0.23	36.4	21.5	7.359	14.8	1.02
28	1	124	[illegible]	738	21.1	24.8	29.8	18.2	0.74	529	0.20	29.8	18.5	7.340	14.7	1.29
	7	111	38	582	16.2	20.3	28.7	15.4	0.76	423	0.25	31.5	22.1	7.402	14.0	1.12
29	1	120	44	674	15.3	23.9	28.2	17.2	0.72	416	0.27	36.0	20.0	7.332	17.1	1.06
	6	113	[illegible]	531	18.3	20.5	25.9	15.5	0.78	370	0.21	36.6	20.4	7.337	17.0	0.79
30	1	88	[illegible]	605	17.8	22.5	28.9	14.8	0.68	399	0.25	32.5	20.0	7.367	18.8	1.22
	7	118	[illegible]	513	17.7	21.3	24.1	14.7	0.69	373	0.18	34.1	25.0	7.387	14.6	—
	1	116	40	627	15.7	22.4	28.0	15.4	0.69	383	0.28	35.1	23.7	7.411	15.1	0.93
	7	109	30	537	17.9	20.5	26.1	15.4	0.75	340	0.33	39.7	23.0	7.350	13.6	1.07
	1	115	[illegible]	630	14.0	22.0	28.6	15.3	0.69	390	0.32	38.6	21.0	7.337	14.2	0.92
	7	122	44	775	17.6	23.7	32.7	19.5	0.82	420	0.36	40.8	23.3	7.354	12.5	0.96
	1		40	782	19.5	26.0	30.0	17.7	0.63	508	0.76	30.6	20.2	7.392	14.1	0.61

TABLE 3.

Intrapulmonary gas exchange data, physiological and anatomic shunts (VI)

No.	Age days	P_{AO_2} mmHg	D_{LCO} ml/mmHg/min	$P_{AO_2} - P_{cO_2}$ mmHg	P_{aO_2} mmHg	$P_{AO_2} - P_{aO_2}$ mmHg	Qs/Qphys per cent	P_{aO_2} mmHg (breathing pure oxygen)	$P_{AO_2} - P_{aO_2}$ mmHg (breathing pure oxygen)	Qs/Qanat per cent (breathing pure oxygen)	phys—anat shunt per cent	Qest ml	$\dot{V}_A$ meas / $\dot{Q}$ est
1	1	97	—	—	72	25	17.3	602	76	6.3	11.0	914	0.55
	6	102	—	—	72	30	17.3	603	66	5.5	11.8	600	0.64
2	1	103	2.1	8	63	41	27.7	536	132	10.5	17.2	589	0.70
	7	100	1.7	13	62	37	28.0	507	158	12.3	15.7	791	0.63
3	1	98	2.8	4	78	21	15.4	614	58	4.9	10.5	397	0.61
	7	104	1.7	11	84	20	11.4	591	64	5.1	6.3	523	0.64
4	1	100	2.9	7	71	29	16.9	634	52	4.4	12.5	694	0.58
	7	104	2.9	5	73	31	15.5	573	88	7.2	8.3	491	0.68
5	1	92	2.9	10	82	11	8.0	643	46	3.9	4.1	991	0.49
	7	100	1.6	9	74	26	19.1	606	68	5.7	13.4	500	0.61
6	1	103	2.0	9	73	30	19.1	592	96	7.8	11.3	397	0.64
	7	101	2.0	10	71	29	18.6	553	124	9.9	8.7	671	0.60
7	1	104	2.1	10	71	33	21.9	585	100	8.1	13.8	720	0.63
	7	107	2.0	11	75	32	18.5	533	133	10.5	8.0	746	0.76
8	1	106	2.0	8	66	40	27.6	526	170	13.1	14.5	534	0.62
	7	108	2.0	8	83	26	13.2	515	162	12.5	0.7	586	0.79
9	1	103	1.4	14	68	35	25.6	526	144	11.3	14.3	697	0.68
	7	106	1.2	14	74	31	18.6	498	169	13.4	5.2	591	0.75
10	1	100	—	—	68	32	22.7	473	202	15.2	7.5	683	0.61
	7	106	—	—	71	35	20.9	453	218	16.2	4.7	614	0.68
11	1	109	—	—	72	37	22.2	550	132	10.5	11.7	849	0.67
	7	104	—	—	68	36	26.0	479	198	14.9	11.1	760	0.69
12	1	100	—	—	68	32	25.6	508	167	12.9	12.7	794	0.60
	7	96	—	—	65	31	25.7	454	214	15.4	10.3	846	0.57
13	1	89	—	—	62	27	29.2	450	231	17.0	12.2	829	0.47
	7	107	2.7	8	68	41	29.4	429	252	18.3	11.1	700	0.77
14	1	95	—	—	63	33	28.8	495	181	13.8	15.0	657	0.54
	7	98	2.5	[illegible]	63	34	28.7	462	203	15.2	11.5	554	0.92

15	1	100	1.4	15	80	20	12.7	559	117	9.4	3.3	723	0.61
	7	105	1.6	13	81	24	10.1	555	117	9.4	0.7	720	0.69
16	1	108	1.8	10	68	42	26.2	657	109	8.8	17.4	657	0.68
	7	111	1.9	10	68	43	24.3	555	154	15.6	8.7	646	0.72
17	1	114	1	10	68	46	29.0	532	159	12.3	18.7	583	0.80
	6	103	1.5	15	67	35	25.2	523	174	12.2	13.0	754	0.63
18	1	102	1.5	12	75	28	19.0	598	85	7.0	12.0	603	0.60
	7	101	1.7	9	78	23	18.0	447	212	15.8	0.2	563	0.62
19	1	105	2.4	7	84	22	13.5	550	135	10.7	2.8	569	0.64
	7	108	2.5	7	82	24	14.7	602	68	5.5	9.2	643	0.72
20	1	107	2.5	8	89	18	8.4	608	69	5.7	2.7	663	0.71
	7	110	1.9	10	91	19	7.4	638	48	4.1	3.3	671	0.69
1	1	105	2.0	11	67	38	26.9	585	108	8.7	18.2	766	0.63
22	1	111	—	—	67	44	19.8	608	83	6.7	13.1	800	0.73
23	1	110	1.9	12	70	39	25.1	494	189	14.4	10.7	786	0.74
24	1	101	2.4	9	72	29	19.9	606	77	6.4	13.5	769	0.57
	7	100	2.1	6	89	11	5.9	613	60	5.0	0.9	443	0.61
25	1	103	2.3	10	67	36	25.8	588	93	7.6	18.2	800	0.62
	7	103	2.0	11	70	33	22.8	512	166	12.8	9.8	788	0.63
26	1	107	3.1	8	69	38	22.9	573	101	8.2	14.7	660	0.71
	6	98	2.4	10	73	25	18.7	540	131	10.4	8.3	814	0.57
27	1	109	2.6	7	63	44	25.8	582	95	7.8	18.0	663	0.74
	7	101	2.4	8	69	32	10.3	555	106	8.6	1.7	691	0.66
28	1	108	2.8	7	73	35	19.0	627	90	4.3	15.4	709	0.75
	7	110	2.8	6	75	35	17.5	631	58	4.9	12.6	580	0.73
29	1	99	2.2	9	76	23	17.8	606	62	5.2	12.4	683	0.61
	6	103	2.7	6	76	26	17.7	638	50	4.2	13.5	586	0.63
30	1	103	1.8	10	76	27	17.7	633	59	5.0	12.7	643	0.62
	7	101	1.4	12	74	27	17.0	617	57	4.8	12.2	609	0.61
31	1	99	2.3	8	67	32	23.2	585	88	7.2	16.0	640	0.60
	7	99	2.3	7	69	30	19.9	544	129	10.3	9.8	586	0.58
32	1	95	1.2	15	66	30	21.9	607	82	5.2	16.7	629	0.56
	7	102	1.3	14	69	33	18.7	468	210	15.7	3.0	677	0.62
33	1	109	2.3	9	91	17	7.9	665	35	3.0	4.9	743	0.68

TABLE 3.

Intrapulmonary gas exchange data, physiological and anatomic shunts (VI)

No.	Age days	P_{AO_2} mmHg	D_{LCO} ml/mmHg/min	$P_{AO_2}-P_{cO_2}$ mmHg	P_{O_2} mmHg	$P_{AO_2}-P_{aO_2}$ mmHg	Qs/Qphys per cent	P_{aO_2} mmHg (breathing pure oxygen)	$P_{AO_2}-P_{O_2}$ mmHg (breathing pure oxygen)	Qs/Qanat per cent (breathing pure oxygen)	phys—anat shunt per cent	Qest ml	$\dot{V}_A$ meas / Q est
1	1	97	—	—	72	25	17.3	602	76	6.3	11.0	914	0.55
	6	102	—	—	72	30	17.3	603	66	5.5	11.8	600	0.64
2	1	103	2.1	8	63	41	27.7	536	132	10.5	17.2	589	0.70
	7	100	1.7	13	62	37	28.0	507	158	12.3	15.7	791	0.63
3	1	98	2.8	4	78	21	15.4	614	58	4.9	10.5	397	0.61
	7	104	1.7	11	84	20	11.4	591	64	5.1	6.3	523	0.64
4	1	100	2.9	7	71	29	16.9	634	52	4.4	12.5	694	0.58
	7	104	2.9	5	73	31	15.5	573	88	7.2	8.3	491	0.68
5	1	92	2.9	10	82	11	8.0	643	46	3.9	4.1	991	0.49
	7	100	1.6	9	74	[illegible]	19.1	606	[illegible]	5.7	13.4	500	0.61
6	1	103	2.0	9	73	30	19.1	592	96	7.8	11.3	397	0.64
	7	101	2.0	10	71	29	18.6	553	124	9.9	8.7	671	0.60
7	1	104	2.1	10	71	33	21.9	585	100	8.1	13.8	720	0.63
	7	107	2.0	11	75	32	18.5	533	133	10.5	8.0	746	0.76
8	1	106	2.0	8	66	40	27.6	526	170	13.1	14.5	534	0.62
	7	108	2.0	8	83	26	13.2	515	162	12.5	0.7	586	0.79
9	1	103	1.4	14	68	35	25.6	526	144	11.3	14.3	697	0.68
	7	106	1.2	14	74	31	18.8	498	169	13.4	5.2	591	0.75
10	1	100	—	—	68	32	22.7	473	202	15.2	7.5	683	0.61
	7	106	—	—	71	35	20.9	453	218	16.2	4.7	614	0.68
11	1	109	—	—	72	37	22.2	550	132	10.5	11.7	849	0.67
	7	104	—	—	68	36	26.0	479	198	14.9	11.1	760	0.69
12	1	100	—	—	68	32	25.6	508	167	12.9	12.7	794	0.60
	7	96	—	—	65	31	25.7	454	214	15.4	10.3	846	0.57
13	1	89	—	—	62	27	29.2	450	231	17.0	12.2	829	0.47
	7	107	2.7	8	66	41	29.4	429	252	18.3	11.1	700	0.77
14	1	95	—	—	63	33	28.8	495	181	13.8	15.0	657	0.54
	7	98	2.5	8	63	34	28.7	462	203	15.2	11.5	554	0.60

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BY HANS JÖRGEN ANDERSEN

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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This survey is based on the following communications, which constitute a part of a research project in progress concerning clinical bacteriologic immunologic and therapeutic aspects of urinary tract infections in infancy and childhood.

I WINBERG J., ANDERSEN H J HANSON L. Å. and LINCOLN K Studies of urinary tract infections in infancy and childhood I. Antibody response in different types of urinary tract infections caused by coliform bacteria. *Brit Med J II* 524 1963

II. ANDERSEN H J HANSON L. Å LINCOLN K. ØRSKOV I ØRSKOV F and WINBERG J Studies of urinary tract infections in infancy and childhood. IV Relation of the coli antibody titre to clinical picture and to serological type of the infecting *Escherichia coli in acute uncomplicated urinary tract infections* *Acta Paed Scand 54* 247 1965

III ANDERSEN H J LINCOLN K. ØRSKOV F ØRSKOV I. and WINBERG J Studies of urinary tract infections in infancy and childhood. V A comparison of the coli antibody titer in pyelonephritis measured by means of homologous urinary and fecal E. coli antigens. *J Pediat 67* 1073 1965

IV ANDERSEN H J BERGSTRÖM T LINCOLN K ØRSKOV F ØRSKOV I. and WINBERG J Studies of urinary tract infections in infancy and childhood. VI. *Determination of coli antibody* titers in the diagnosis of acute urinary tract infections lacking the usual urinary findings. *J Pediat 67* 1080 1965

V ANDERSEN H J Studies of urinary tract infections in infancy and childhood. VII The relation of E. coli antibodies in pyelonephritis as measured by homologous and common (Kunin) antigens. *J Pediat 68* 542 1966

VI ANDERSEN H. J Studies of urinary tract infections in infancy and childhood. IX. Determination of E coli antibodies by a polyvalent antigen. *Acta Paed Scand* In press

These communications will be referred to as I—VI

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INTRODUCTION

Most of the studies hitherto published on the pathogenesis of urinary tract infection in childhood are concentrated on anatomical abnormalities, mainly congenital and acquired obstructions, and on the question of nephropathogenicity of certain bacteria. Although immunologic mechanisms are known to play an important role in the defence against infectious diseases and can influence their course surprisingly scarce information has until recently been available on the immune response of patients with urinary tract infections. Further this information is to some extent controversial. This may at least in part, depend upon the heterogeneity of the materials investigated comprising obstructed and nonobstructed, first-time and recurrent infections in both sexes and in patients of very different ages.

For this reason we found it necessary to study the antibody response in a strictly defined material of children with first-time urinary tract infections. As the passive haemagglutination method, commonly used for determining the antibodies in the patients sera, is dependent upon the use of antigens derived from the infecting bacterial strains, it is too complicated for clinical routine and it was thus judged important to search for alternative antigen sources.

It is the aim of the present investigation to answer the following questions

1. What is the normal course of the antibody response measured by means of the passive haemagglutination method, during an acute urinary tract infection
   a) with signs of renal involvement
   b) without signs of renal involvement
   c) with regard to the age of the patient
2. Which alternative antigen sources may be employed as substitutes for the infecting urinary bacteria.

Further it will be shown that determination of the antibody titres may be used to

a) differentiate pyelonephritis from lower urinary tract infection in doubtful cases,

b) diagnose pyelonephritis in suspected cases with inconclusive urinary findings,

c) demonstrate the etiology in obscure cases, where chronic pyelonephritis may be a possibility

d) illustrate some immunologic relationships between mother and newborn.

METHODOLOGIC STUDIES

The method used for determination of antibodies to *E coli* throughout this investigation was the technique of passive haemagglutination. This method is based on the principle that certain bacterial antigens are adsorbed to red blood cells and thereby become agglutinable by the antibacterial antibodies. It was first described by Keogh North and Warburton in 1947 (11) for the determination of agglutinins to the *Haemophilus* group It has later been adopted by several investigators for use in different infections, for instance tuberculosis by Middlebrook and Dubos (21) and Lagercrantz (16) streptococcal infections by Kirby (12) and for *E coli* originally by Hayes (9)

A thorough investigation of the influence of variations of the passive haemagglutination technique on its specificity was published by Madsen in 1954 (20) He found that sheep erythrocytes were most suitable for the haemagglutination reaction as they gave stable suspensions and distinct agglutination patterns with clear-cut titre limits After sensitization the cells could be stored for several days at 4–6 C. He found that the haemagglutination reaction was highly specific since the red cells sensitized with extracts of *E coli* were agglutinated only by the homologous 0-group antiserum This however is not quite true as some crossreactions exist between certain 0-groups This was shown by Kunin and Beard (16) who in 1963 presented a survey of the relation between most of the known *E coli* 0-antigens and their corresponding antisera. They were able to demonstrate a limited number of cross reactions between some 0-antigens.

The high specificity of the passive haemagglutination reaction was verified in the present study It has been observed repeatedly that antigens, prepared from *E coli* belonging to another 0-group than the one found in the actual patient's urine gave haemagglutination titres only within the normal limits whereas with the antigen from the infecting bacterial strain elevated titres were found Similar results were obtained when sera were tested with antigens derived from the same bacterial strains isolated from the urine at different episodes of urinary tract infections. Further haemagglutination inhibition experiments have clearly demonstrated that the haemagglutination reaction of red blood cells sensitized with a certain antigen will always be completely inhibited by preincubation of the serum with the same antigen but not with an antigen of a different 0-type It is thus of vital importance for the reliability of the method that the antigen employed is derived from the same *E coli* 0-group as the one infecting the patient or at least has a close antigenic relationship to this type In this study therefore the patients sera were generally tested with antigen derived from their own urinary bacteria

Storing of sera

Early during this study it was noticed that high titres found in the sera within a few days after the sample collection could not be reproduced when the sera

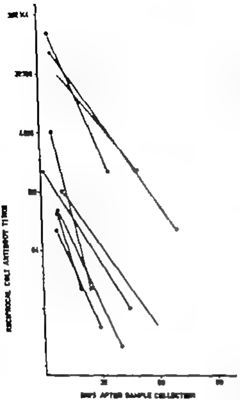


Fig. 1. Nine serum samples titrated with their corresponding antigens shortly after the sample collection and again one to two months later. The sera were in the mean-time stored at +4 °C.

Table I. Monthly titrations of 7 sera stored at temperature of −20 °C. The results are expressed as titration steps.

Serum	Months after sample collection						
	0	1	2	3	4	5	6
1	13	13	15	13	14	13	[illegible]
2	12	10	13	13	11	12	12
3	17	17	18	17	17	17	18
4	10	17	16	18	[illegible]	16	—
5	15	16	16	15	16	16	17
6	12	13	12	13	12	11	12
7	16	15	15	16	17	16	—

were titrated again after about one month (Fig. 1). The sera were in that stage of the investigation kept in a refrigerator at +4 °C. To test the importance of the temperature some sera were kept at −20 °C and titrated once a month for five or six months. The results are presented in Table I, which shows that for the period of time studied the sera preserved their antibody activity. Since then all sera were stored at −20 °C till used.

Antigen studies

A. Antigen preparation and concentration. For sensitization of the sheep erythrocytes the supernatant of a centrifuged boiled suspension of the actual bacteria was used as described by Neter *et al.* (22) and presented in detail in I.

In most of the experiments the concentration of the antigen was standardized by comparison of the unboiled bacterial suspension to a McFarland scale and adjusting the concentration to about 1200 million bacteria per ml. In the experiments with polyvalent antigen (VI) equal parts of eight antigen suspensions of different O-types of this strength were mixed and the concentration of each antigen was thus reduced to about 150 million per ml. To ascertain that this concentration was sufficient to obtain the same titres, a series of titrations of sera with erythrocytes, sensitized with different dilutions of the homologous antigens, were performed. The results are presented in Table II from which it appears that dilutions to 1:20 (equal to [illegible] million bacteria per ml) still gave the same results as undiluted antigen suspensions. Thus each separate antigen was still present in excess when used in the polyvalent antigen. The results

Table II Titrations of 5 sera with sheep erythrocytes sensitized with homologous antigens in different dilutions. Undiluted antigens are derived from a stock containing about 1200 million bacteria per ml. The results are expressed as titration steps.

Serum	Antigen dilutions 1:1	1:5	1:10	1:20	1:30	1:40	1:50	1:100
1	9	10	10	9	6	4	3	1
2	14	14	14	14	8	6	—	1
3	15	14	15	15	10	8	4	1
4	15	15	16	15	9	9	5	1
5	13	13	1	13	8	7	6	1

obtained by means of the polyvalent *antigen can therefore be regarded as* comparable to those found with the individual antigens.

B Sources of antigen The main part of the methodologic studies during this investigation was devoted to the possibility of using antigen sources other than the infecting urinary strains This was of interest mainly for two reasons. *Firstly* because it was found necessary to find an adequate substitute for the urinary bacteria in cases suspected of urinary tract infections, but with negative urinary cultures Secondly it was deemed of practical value if it were possible to exclude the time-consuming and vulnerable process of preparing antigens from the strain isolated from each patient s urine for the study of the antibody response

1 F a e c a l c o l i a n t i g e n s (III) The background for these experiments were the findings of Turck *et al* (20) and Vosti *et al.* (32) that the serologic type of *E coli* found in the urine from patients with urinary tract infections was usually also present in their faeces and, in most cases identical with the *predominant* strain there To verify this, the antibody titres of a series of pyelonephritic patients were determined simultaneously with antigens derived from strains isolated from urine and faeces from each patient The results were compared to the results of serological typings of the strains from *both sources It was found that the faecal* bacteria might be used for antigen preparation with some success but the frequency of positive findings were lower than when the urinary strains were employed This was due to the fact that the frequency of identical serotypes in urine and faeces was considerably lower in our *patients than the frequency found by the* previously mentioned authors. This may at least partly depend upon differences in technique as described in detail in III

2 C o m m o n e n t e r o b a c t e r i a l a n t i g e n (V) In consequence of the partly unsatisfactory results of the use of the patients faecal bacteria the interest was focused on the common enterobacterial antigen, accidentally discovered by Kunin *et al* in their studies of cross reactions between different *E coli* O-antigens and their antisera (16) During this study they found that antisera to O14 O50 O124 and O144 gave haemagglutination reactions with almost all *E coli* O-antigens and with antigens prepared from other *Enterobacteriaceae* as well

A crude preparation of the common enterobacterial antigen, prepared from *E coli* O14 which contains the greatest amount of this antigen (15) was used for sensitization of sheep erythrocytes and a series of patients were tested longitudinally with this antigen simultaneously with antigens derived from the infecting bac-

teria from these patients. The results showed clearly that the common antigen could not substitute the homologous antigens. Almost all patients sera were found to have low titres against the common antigen, but only two out of 22 had variations in this titre and these variations were very slight. Further it appeared from this investigation, that antibodies to the common enterobacterial antigen did not interfere with the determinations of antibodies to the homologous urinary or faecal bacterial strains. This conclusion was based on haemagglutination-inhibition experiments, showing very slight or absent reduction of the antibody titres determined by means of the O-antigens of the infecting strains in sera, preincubated with the aforementioned preparation of the common antigen.

3 Polyvalent E. coli antigen (VI). Experiments with antigens other than the homologous urinary strains, were also performed with erythrocytes simultaneously sensitized with eight different *E coli* O-antigens. The experiments were based on the findings of several authors (7 25 27 29 32) who showed that relatively few O-groups of *E coli* are responsible for most of the urinary tract infections observed in the patients. Thus, it appeared possible to detect the antibodies in most patients if the carrier cells could be sensitized with a sufficient number of different *E coli* O-antigens.

To investigate this, a series of experiments were performed with rabbit *E coli* antisera, titrated with erythrocytes coated with varying numbers and combinations of different *E coli* O-antigens. It was found that not only could at least eight antigens be simultaneously adsorbed to the red blood cells, but the reactions obtained were of the same magnitude and of the same specificity as when the antigens were used individually

The specificity of the reaction with the polyvalent antigen were confirmed in a series of clinical experiments. The titres against the polyvalent antigen was found to run a course parallel to the titres of the homologous antigen in those cases where the homologous antigen belonged to one of the O-groups, included in the polyvalent antigen.

This modification of the method for determining antibodies to *E coli* seems to offer a reliable alternative to the original method and to make it easier to utilize antibody determinations in clinical routine. At the same time it is a readily available and adequate instrument for use in sera from patients who for various reasons have negative urinary cultures.

Accuracy of titration results All titrations of sera from patients and controls were performed in twofold serial dilutions of the sera and were made in duplicate A good correlation was found between these double determinations (Fig 1 in II)

Because of the extremely high titres found in several sera it was regarded necessary to check the precision of the serial dilutions. For this purpose a twofold serial dilution of serum containing an amount of J[131] was prepared, using one pipette for each serum as in the routine titrations and the dilutions of the isotope were determined in a Geiger-counter In this way it was found that, within a confidence limit of 95 per cent, the dilution factor was between 0.5 and 0 6 with a mean value of 0.55 (9a)

This error means that the titres will be

read slightly higher than the true titres are With a dilution factor of 0.55 instead of the intended 0.5 a true titre of 128 will be read one step too high (i e. 256) and a true titre of 32 768 two steps too high. However the tests performed show that the error is very constant and thus of minor importance.

ANTIBODY TITRES TO E COLI IN UNINFECTED CHILDREN

A survey of the literature published before these studies were begun gave only scanty information concerning the presence of *E coli* antibodies in uninfected children. Using passive haemagglutination, Neter *et al* (24) determined the antibody titres against the enteropathogenic strains 026 055 and 0126 in 323 sera mainly from infants and children and found that the titres increased with the age. Of more interest to this study is the publication by Kunin (14) where he tested sera mainly from children against six of the 0-groups commonly encountered in urinary tract infections (01 02 04 06 07 and 075) Even in this study increasing titres with age could be demonstrated.

In the present study the antibody titres were determined in three series of children (II, V VI) without infections, past or present, in the urinary tracts The children investigated for this purpose were carefully selected according to the following criteria.

1 No history of previous urinary tract infections or repeated unexplained febrile episodes.
2 Normal temperature and sedimentation rate at the time of the sample collection.
3 Less than 1000 microorganisms per ml of urine at the time of the sample collection.

The results of the titrations in these controls were presented in II V and VI In II sera from 80 children were tested with *E coli* antigens prepared from the childrens own faecal flora This was regarded as the most adequate antigen source for comparison with the titres in the patients, where the antigen source was their urinary bacterial flora as it is generally assumed (29 32 34) that the coli bacteria invading the urinary tract originate from the intestinal flora.

In V the 36 controls were tested with their own faecal bacterial antigens as well as with a crude preparation of Kunin s common enterobacterial antigen derived from a strain of 014

Thus a total of 116 sera from healthy controls were tested with antigens derived from their own faecal *E coli* flora and it was found that almost all children above the age of two months possessed antibodies against these antigens. The maximum titre found in any of the controls was 128 which was found in one child. All other sera had titres of 64 or less. In the eleven infants below two months of age in these two groups no antibodies were found in eight, while three had titres of 2 16 and 64 respectively

The antibody titres to the common enterobacterial antigen were lower than

or—in four cases—equal to the titres determined with the antigens from their faecal coli strains.

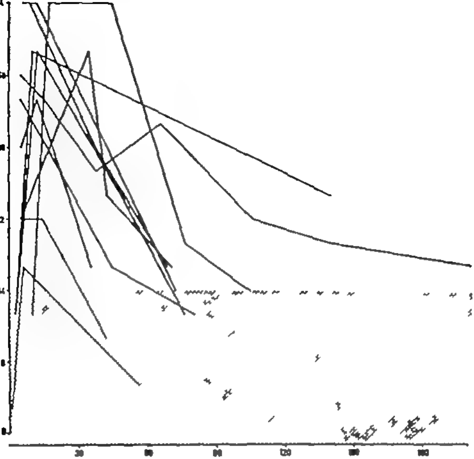
In study VI, 133 controls were tested with erythrocytes, simultaneously sensitized with eight of the O-antigens, most commonly encountered in urinary tract infections. The titres against this polyvalent antigen showed the same general trend as the titres found with the antigens from the patients faecal coli strains i.e. very low in early life and increasing throughout the age period studied. It is somewhat surprising to find that the titres found by means of the polyvalent antigen are generally higher than in the controls tested with their faecal bacterial antigens. It is less probable that the titres obtained with several antigen bound to the same erythrocytes will be the sum of the titres against each of the antigens. It would rather be expected that the titre determined with the polyvalent antigen would be identical with the highest titre to anyone of the individual antigens. This would be in agreement with observations in patients with urinary tract infections in theses studies (Fig 4 in IV) As the bacterial antigens included in the poly valent antigen represent the most commonly encountered bacterial strains not only in the urinary tract, but also in the faecal flora (29 32) it is possible that most of the control cases have for long periods of time harboured one or more of these bacterial types in their intestinal tracts and have therefore been exposed to a long-standing stimulation to antibody production against these

ANTIBODY TITRES IN PATIENTS WITH ACUTE, UNCOMPLICATED URINARY TRACT INFECTIONS

One of the problems met with in the diagnosis and clinical management of urinary tract infections is the difficulty of judging whether an infection involves the kidney or not. It is generally accepted that febrile urinary tract infections are usually combined with renal infection, but the frequent absence of fever or any general symptoms at all, in patients with chronic pyelonephritis makes it obvious that diagnosis of cystitis cannot be justified before renal involvement has been excluded by means of laboratory methods It was therefore judged of interest to see whether a difference existed between the antibody responses in urinary tract infections with and without renal involvement To investigate this, the antibody titres were determined in a series of patients with acute uncomplicated urinary tract infections (I II)

The diagnosis was based on the clinical symptoms and urinary findings of leucocytes and bacteria in significant amounts. The disease was defined as pyelonephritis in patients with fever elevated sedimentation rate and impairment of the renal concentrating capacity during the acute phase, and as cystitis only if all of the three above-mentioned signs were absent.

The studies showed that the patients above three months of age with pyelonephritis almost invariably had a marked increase in the antibody titre against the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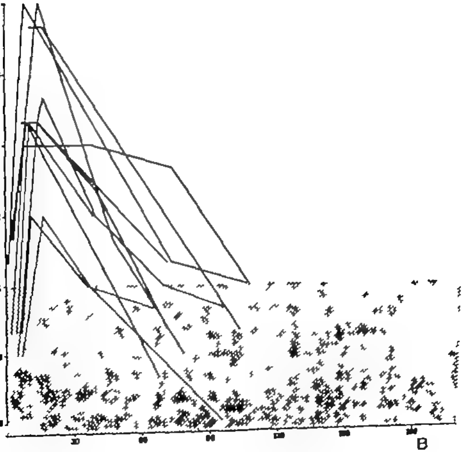
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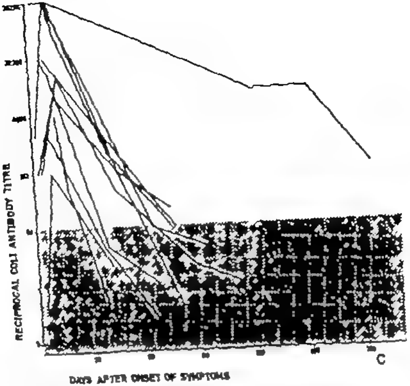

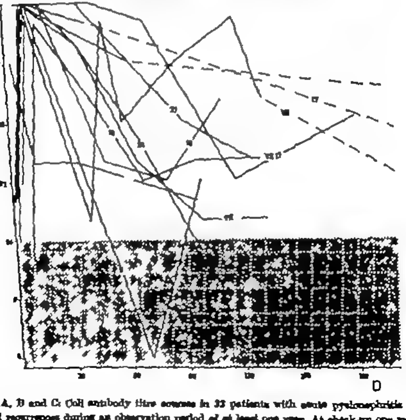

Fig. 2. A, B and C: Coli antibody titre courses in 33 patients with acute pyelonephritis without signs of recurrences during an observation period of at least one year. At check-up one year after the onset of symptoms the titres were normal in all cases except one.

Fig. 3 D: Titre courses in 11 patients with acute pyelonephritis and

infecting strain. In the patients with cystitis, on the other hand the titres remained within the range found in the controls Thus it appears that the determination of the antibody response in patients with urinary tract infections is a useful tool in differentiating between patients with pyelonephritis and with cystitis.

This unfortunately does not hold true in infants below the age of two months. During this investigation antibody titres were determined in sera from 30 infants of this age group (1) Although most of these patients in addition to their urinary findings had signs of serious infections such as extreme weight loss (more than 10 per cent of the body weight) vomiting and in several cases, severe septic infection with positive blood culture the titres obtained were generally very low One patient, aged 50 days had a titre of 4000 while in the rest of the cases the maximal titre found was 64. In only seven other infants significant rises of threefold increase in titre could be observed in consecutive samples

The reason for this is not clear It is generally agreed upon that newborn babies are able to produce antibodies of this type In a recent paper Florman and Lambertson (6) demonstrated production of antibodies to E coli 04 in three premature infants infected with this type Lodinova et al (19) found significant titre rises in the serum of newborn infants to E coli 083 after artificial colonization of the intestinal tract. On the other hand, when they determined the antibody titres against antigen from the spontaneously occuring bacterial flora of the faeces they found very low titres

One explanation for the lacking antibody response to E coli infection observed in the infants may be that the infections are caused by bacteria colonizing the mother and against which she has produced antibodies. IgG antibodies are known to be able to pass from the mother to the foetus via the placenta. Their presence in the infant s blood at the time of the infection may inhibit the production of IgM antibodies (8)

In several bacterial or viral infections serologic reactions show a certain relationship to the course of the disease and are thus helpful in the evaluation of the outcome of different therapeutic measures and of the disease itself

It was therefore found of interest to investigate the relation between the clinical course of the disease and the pattern of the antibody response

For this purpose the 58 patients with pyelonephritis included in studies II and V were selected Thirty three of these patients followed for at least one year (in most cases more than three years) did not during this observation period show any signs of recurrence symptomatic or asymptomatic. The antibody titres determined during their illness and convalescence are given in Figs. 3 A, B and C It appears from these that the titres had their maximum between 5 and 15 days after the onset of the symptoms and that they with a few exceptions fell to normal values within 90 days Three patients in this group show a definitely delayed decrease in the antibody titres. They are still being followed, but have not shown any traditional signs of recurrence or chronic disease One of these patients still have an elevated titre more than three years after the infection. The other 32 patients

Table III Findings in 11 patients with their first recurrence after an acute pyelonephritis. The courses of the antibody titres are illustrated in Fig. 2 D

Patient no.	Time after initial infection	F brile (+) or afebrile (−) recurrence	Serotype at initial infection	Serotype at recurrence
6	3 months	+	06: :H4	02: :H2
14	8 months	+	01 :H–[a]	Klebsiella
15	3 months	−	06: :H4	075: :H
16	3½ months	+	02: :H4	Strept. faecalis
17	11 months	+	01 :H–	ND[b]
18	4 months	−	06: :H4	06: :H4
24	36 months	+	04: :H?[c]	ND
27	3 months	+	085: :H11	Enterococci
VII 4	2 months	+	06: :H7	06: :H4
VII 8	3 months	−	06: :H4	06: :H4
VII 17	6 months	+	075: :H10	rough: :H17

[a] 01 :H– means *E. coli* O-antigen 1 and immotile, no H-antigen. The empty space between the two colons is for the K-antigen. The K-antigens were not examined in this study

[b] ND = not done.

[c] H? means motile, but not agglutinated with the established 49 H test sera.

in this group had normal titres at a check-up one year after the infection.

Agglutination methods favour the demonstration of IgM antibodies (8). Although IgG antibodies against the coli O-antigens can also be shown, IgM antibodies are generally assumed to dominate the antibody response to this antigen (8). The half life of IgM antibodies is about 5 days (3) and it is suggestive that the decrease in the antibody titres in the patients treated for acute pyelonephritis goes well with such a catabolic rate. Since IgM antibodies are assumed to be formed only in the presence of antigen (30) the rapid decrease of antibody titres in most of the patients in Figs. 2 A, B and C might indicate that the bacterial antigens are effectively eliminated by the treatment.

Out of the 58 pyelonephritic patients in studies II and V 11 have had recurrences during the observation period. Some relevant findings in these patients' recurrences are presented in Table III and the titres obtained are illustrated in Fig. 2 D. A comparison between the courses of the antibody titres in the patients with and without recurrences shows two noteworthy findings. First, it is obvious

infecting strain. In the patients with cystitis on the other hand the titres remained within the range found in the controls. Thus it appears that the determination of the antibody response in patients with urinary tract infections is a useful tool in differentiating between patients with pyelonephritis and with cystitis.

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inconclusive. It is of course difficult to be completely certain of the diagnosis of pyelonephritis even when this immunologic reaction is positive since a finding of an elevated antibody titre to a certain bacteria only demonstrates that the patient is infected with this strain, but not that this infection is localized to the kidneys. It is known that infections with *E coli* such as enteritis (23) and appendicitis (31) may elicit antibody responses to the infecting bacteria. However in view of the typical symptoms and findings, in particular the reduced concentration capacity in most of these patients it was regarded as most likely that they were suffering from pyelonephritis. A definite confirmation of the diagnosis might have been obtained by means of the technique employed by Aoki and McCabe (2) who used antiserum to the common enterobacterial antigen for immunofluorescent detection of bacterial antigen in renal biopsy specimens.

In study nr IV it was shortly discussed whether these infections differed from the traditional ones in other respects than the sparse urinary findings. It may therefore be of interest to present the findings at reexaminations three years after the original infections. Four of the patients (Cases nr 1 2 4 and 5) have in the meantime been completely free from symptoms from their urinary tracts and were found to be normal on examination including blood pressure readings, haemoglobin, ESR, urinary examination and culture and coli antibody determination. Case 3 had had occasional abdominal pains without fever or micturition symptoms. The antibody titre against the original faecal flora was again found to be elevated (1024) as well as against the polyvalent antigen (2048) All other findings were normal. Case 6 was treated abroad for a urinary tract infection two and a half years after the infection seen here, but at the reexamination she was free from symptoms or abnormal findings. Case nr 7 was again referred to this hospital two years after his first admission because of an elevated blood pressure found on routine examination. He had a blood pressure of 140–160/100–110 and was found to have heart enlargement and hypertensive retinopathy The true endogenous creatinine clearance was normal (170 l/24 h/1 73 m²), while the concentration capacity was slightly reduced (770 mOsm/l) Intravenous pyelography (IVP) showed progress in the parenchymal reduction earlier observed on both sides Repeated urinary cultures were negative. The coli antibody titres determined against polyvalent antigen as well as against antigens derived from the patient's faecal coli flora were normal. The possible presence of antibody titres against other *E coli* O-types than the eight included in the polyvalent antigen and those found in the patient's faeces was not investigated.

Case nr 8 has on two occasions been investigated because of micturition pains and on both occasions had leucocyturia but negative culture. Coli antibody titres were normal against the earlier employed urinary bacterial antigen and the polyvalent antigen.

Of these eight patients one has contracted serious renal damage consistent with the sequelae of pyelonephritis; another has had a recurrence, not observed here, and two have had minor symptoms,

that the antibody response is not less in the former group or in other words, the cause of the recurrences in these patients without macroscopic malformations in their urinary tracts could not be a deficient antibody response measured by the present method. It should be emphasized that this of course does not exclude the possibility of differences in other immunologic systems in these two patient groups Secondly it is of interest to observe that 4 of the patients in Fig 2 D and Table III (cases 6 14 16 27) had raised titres against antigens derived at the first infection although the reinfections were caused by a different serotype of *E coli* (case 6) or by different species (case 14 16 and 27) The reason for this phenomenon, which has been observed in other patients (cf. IV case 5) is not clear One possibility however is that it illustrates a latent infection which is reactivated by a reinfection, which may in itself be of minor importance

ANTIBODY TITRES IN PATIENTS WITH ATYPICAL ACUTE PYELONEPHRITIS

The term atypical pyelonephritis is in this survey used to signify cases with signs and symptoms typical for acute pyelonephritis, but lacking the usual urinary findings, i e without significant leucocyturia and bacteriuria That patients with chronic pyelonephritis for long periods of time may not excrete bacteria in the urine is well known (13) In acute cases this is less well recognized although several factors may cause low bacterial numbers in the urine such as presence of bacteriostatics pH below 5.5 very frequent micturitions or obstructions in the urinary tract It is also mentioned by Kass (10) that "abscesses may be produced in the kidney which do not discharge organisms into the tubules. Usually these are associated with manifest clinical evidence of sepsis and renal localization" The existence of such "closed" infections which do not communicate with the pelvis is further substantiated in a recent paper by Deliveliotis *et al* (5) who found abacteriuric renal infections in patients with solitary cysts of the kidneys

Abacteriuric experimental pyelonephritis in rats was recently reported by Schmidt *et al* (28) who injected *E coli* directly into the renal pelvis Urinary samples collected regularly for 8 weeks after the infection was established showed neither pyuria nor bacteriuria in 70 out of 209 samples Two of the 31 rats had completely negative urinary findings on all occasions The diagnosis was finally confirmed by histopathologic examination of the kidneys.

A series of patients of this type was investigated in IV The essential finding in this study was that the antibody titre courses in these patients were similar to those usually observed in pyelonephritic patients with pathologic urinary findings. This supports the diagnosis of pyelonephritis in cases, where the usual urinary findings are lacking or

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Of these eight patients one has contracted serious renal damage consistent with the sequelae of pyelonephritis another has had a recurrence, not observed here, and two have had minor symptoms,

which are difficult to evaluate Nothing in the courses of these case histories differs from the course which might be anticipated in ordinary cases of pyelonephritis.

In these patients with history and symptoms suggestive of pyelonephritis, but with unconvincing urinary findings demonstration of antibodies in elevated titres strengthens the diagnosis. However as no urinary bacteria are available for antigen preparation in these patients it is necessary to obtain a related antigen from some other source This was originally the reason for investigating the patients faecal flora as an antigen source as described earlier

FURTHER CLINICAL USE OF COLI ANTIBODY DETERMINATIONS

Recurrent urinary tract infections

In several patients with urinary tract infection repeated recurrences are observed. In most cases a change of the bacterial flora is found from one infection to the next (4) Some patients of this type were followed for long periods and their symptoms and findings will be illustrated with the following case history

M M ♀ 54 07 16 This patient had her first known urinary tract infection in December 1959 and since then she has had several symptomatic and asymptomatic recurrences. From September 1962 she has been seen regularly at this hospital. September 1962 she was infected with a strain of *E coli* O21 :H19 causing a symptomatic infection and an elevated antibody titre to this strain (Fig 3) Six weeks later she was reinfected with an *E coli* O1:H– with fever and elevated ESR, but without local symptoms. The antibody titre was elevated against this new strain and remained high for a period of four months after which it decreased to only a slightly elevated level. During the period June 1963 to January 1964 the patient was not seen here but was, according to the parents and herself perfectly well. She reappeared for a check up in January 1964 and felt well was afebrile and had an ESR of 12 mm/1 h. In spite of that she was found to have leucocyturia and 1 million *E coli* O1 :H– Again, there was a high antibody titre against this strain. The titre persisted high for about three months and then dropped to a slightly elevated level. In July 1964 she had another asymptomatic infection, now with a strain of *E coli* O18. The titre against this strain remained normal. A new antibody titre rise against the O1-strain was found in November 1964 in connection with a new asymptomatic recurrence caused by O1:H– Since then no bacteria were found on numerous controls and the antibody titre has slowly returned to the normal level.

During the years of her illness, IVP was performed on three occasions. In April 1960 it was completely normal and in December 1962 a dilatation of the left pelvis and ureter was found. In March 1964 the left kidney showed some reduction of the parenchyma and coarse calyces. Urethro-cystography performed on the same occasions never showed any abnormalities, particularly no vesico-ureteral reflux.

In this patient where the findings have been normal for a three year period after a long series of recurrences, it seems likely that a definite healing of the infection has been obtained, although the progressive changes in the IVP may point to a healing with scarring of the left kidney

The following patient shows a constantly increased antibody titre in spite of only one recurrence after a urinary tract infection.

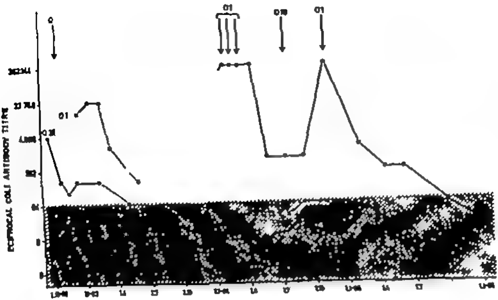

Fig. 3. Coli antibody titres in patient M. M. During the observation period the first infection was caused by *E. coli* O31:H19. The O-types at the recurrences are given in the figure.

E. W. ♀ 42 62 [illegible] This patient had her first known urinary tract infection in December 1960. Although she had no loin or abdominal pain and no micturition symptoms she had fever, heavy leucocyturia and significant bacteriuria. The renal concentrating capacity was reduced. After therapy with sulphonamide she was well with sterile urine. Only 23 days after the cessation of therapy however she got a febrile recurrence with the same serological type of *E. coli*, O6:H7, now resistant to sulphonamide. This infection was treated with nitrofurantoin and the urine was again sterile. In connection with these two infections she was found to have a rather high antibody titre against the infesting strain and the decrease after treatment was very slow (Fig. 4).

She was readmitted in October 1962 by a practitioner who on repeated occasions had found her blood pressure to be 160/80. A hypertension could not be confirmed here and a re-investigation of her kidneys revealed nothing abnormal. However the coli antibody titre was still found to be increased and for this reason she has been seen regularly since then. Her urinary findings have on all occasions been normal without bacteriuria and she has been feeling well. Her blood pressure has been checked on several occasions and found to be somewhat elevated in the range of 140–165/90–105. IVP has been performed on three occasions. In January 1961 the right kidney was observed to be significantly smaller than the left and to have some calyceal dilatation. The findings were similar on the two following examinations in August 1965 and November 1966. Urethrocystography in January 1961 and August 1965 both showed vesico-ureteral reflux with pronounced dilatation of the ureter on the left side and discrete reflux on the right side. Reexamination of the patient in August 1965 showed a concentrating capacity of 1140 mOsm/l, specific plasma creatinine 0.8 mg per 100 ml and true endogenous creatinine clearance 121 l/24 h/1.73 m². In November 1966 the concentration capacity was unchanged, plasma creatinine 1.1 mg per 100 ml and creatinine clearance 105 l/24 h/1.73 m².

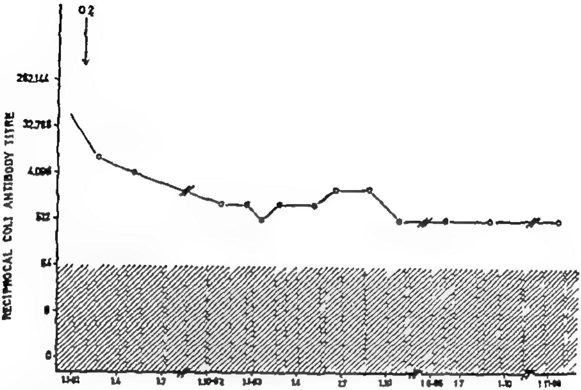

Fig 4 Coli antibody titres in patient *B W* originally infected with *E coli* O2:H7 and having one recurrence, caused by the same serotype. The antibody titre has remained elevated during an observation period of almost six years.

The patient was in repeated periods given sulphonamide up to half a year at the time. *Ampicillin* was given in two periods of two weeks. No effect on the antibody titre could be found after these therapeutic trials.

In summary this patient has had two attacks of acute pyelonephritis caused by the same serological type of *E coli* Since then she has had an elevated antibody titre against the infecting strain in spite of having no bacteriuria Some reduction of the renal parenchyma was observed in connection with the first known infection but this does not appear to progress Her blood pressure has a tendency to be elevated but returns to normal after a few days rest. The renal filtration is slightly reduced, but the concentration capacity normal

The findings in this patient are difficult to evaluate However it seems likely that there is some pathologic process in her renal parenchyma and that coli anti body production is still enhanced. Her tendency for elevated blood pressure makes it possible that she is at risk for having the same evolution of her pyelonephritis as demonstrated by the following patient, G.N

Hypertension

The diagnosis of the underlying disorder in patients with renal hypertension may often be difficult and there is thus a need for complementing procedures. So it was found of interest to see if determi nation of coli antibody titres in hyperten

sive patients were of any use. A series of patients were studied and the results will be published separately (1) The following case history will serve as an example

G N ♂ 11 03 44. At the age of two years this boy suffered from febrile urinary tract infection, caused by coliform bacteria. He was treated for two weeks with sulphonamide and the course was uneventful. A urinary culture performed two days after the cessation of therapy showed sterile urine. An IVP was normal.

During the following years he had several attacks of tonsillitis and at the age of ten he was treated for osteomyelitis. Routine investigations of the urine on several of these occasions revealed nothing abnormal. No cultures were performed, however

At the age of eleven years he was admitted to hospital for tonsillectomy His blood pressure was found to be elevated and he was referred to this hospital.

He was short and lean and had a blood pressure of 180/125 X-ray examination of the heart showed left-sided enlargement. Ophthalmoscopy revealed hypertensive changes of grade II III. Urinalyses Traces of protein, 0–4 leucocytes/mm^3 of uncentrifuged urine. Repeated quantitative urinary cultures <1000 bacteria/ml. Specific plasma creatinine 0.6 mg per 100 ml. True endogenous creatinine clearance 180 1/24 h/1 73 m^2 Maximal renal concentrating capacity 790 mOsm/l. IVP: Reduction of the renal parenchyma bilaterally together with calyceal dilatation. The changes were most pronounced on the right side.

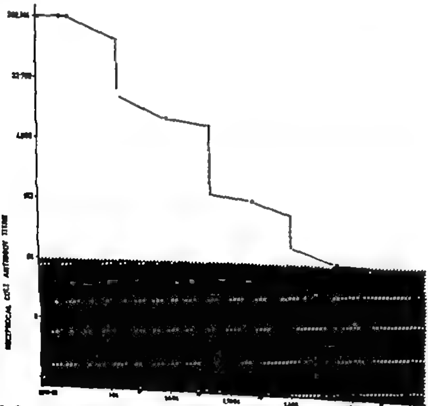

Fig. 5. Coli antibody titres in patient G. N with hypertension, probably caused by pyelonephritis. The antigen was in this case prepared from the patient's faecal coli strains.

As no bacteria were found in the urine, antigens were prepared from the patient's faecal coli flora and extremely high titres were demonstrated against these (Fig 5) Titrations were also performed in some of the serum samples from this patient with antigens derived from *E coli* 01 2 4 6 7 8 14 18 75 and 120 The antibody titres against 08 were similar to those obtained with the antigens derived from the patient faecal bacteria. The titres against the other 0 types were all 64 or less. It is thus most likely that the antibodies were elicited by *E coli* 08

The patient hypertension was treated with antihypertensive drugs continuously and he was further given sulphonamide for a period of about two years. He is still seen at regular intervals and his hypertension has stabilized at about 140/85. Urinary cultures performed at the check-ups have always been negative. There has been a slow but significant decrease of the antibody titre (Fig. 5)

The very frequent throat infections suffered by this patient arose the question of whether it could have been a covert glomerulonephritis which caused the hypertension. However the normal filtration, the slightly reduced concentration capacity and the roentgenologic findings made it more likely that the cause was a chronic pyelonephritis probably originating from his infection at two years of age This diagnosis is supported by the demonstration of an intense antibody response which decreased during chemotherapy

The reason for the long-standing elevations of the antibody titres in the preceding two patients is not quite clear As earlier pointed out the antibodies found with the haemagglutination method are mainly IgM and it must be assumed that antigens are still present in some form to stimulate the antibody producing cells. This may be in the form of a chronic infection with ordinary bacteria. It may also be caused by bacterial variants, not growing on the usual bacteriologic media Finally it may be caused by amorphous bacterial antigen remaining in the kidneys after an infection as recently found by Aoki and McCabe (2)

The findings in these patients indicate that determination of the antibodies may be an important tool as it seems to offer a possibility to detect some patients with early chronic pyelonephritis

Asymptomatic bacteriuria

So far there are very few reports of coli antibody determinations in patients with asymptomatic bacteriuria. In their extensive study of urinary tract infection in school children Kunin *et al* (17) determined the antibodies to *E coli* O-antigens in some of the bacteriuric children, but did not find significant elevations in any Percival *et al.* (20) found elevated antibody titres in 32 per cent of a group of pregnant women with asymptomatic bacteriuria

In the present study no systematic investigation of asymptomatic bacteriuria was attempted, but several titrations were performed in patients with asymptomatic recurrences found on routine examinations after acute urinary tract infections. In these situations elevated antibody titres were often found Examples of this were presented earlier (Fig 3 and Table III Cases 15 19 and VII 5)

Another patient with asymptomatic bacteriuria was found during the collection of samples from controls The case history is presented below

B. A. ♂ 62 11 30 The patient was readmitted at the age of five months for check-up after convulsions in the neonatal period, caused by minor cerebral bleeding. He was found to have slight neurologic sequelae, but was normal from other points of view He was af brile, had normal appetite and weight gain, haemoglobin 11.7 g per cent, ESR 4 mm/1 h. Urinary leucocyte count 14/mm³ Repeated quantitative urinary cultures revealed growths of 90,000–700,000 *E* coli/ml. His renal concentration capacity was 565 mOsm/l, which is slightly reduced with regard to the age (33). He was treated with sulphonamide, after which the urine was sterile and the concentration capacity rose to normal values. The coli antibody titres in this patient are presented in Fig 6 which shows an increased antibody titre when the disease was detected and normal fall after the treatment.

In spite of the complete absence of general symptoms it appears reasonable to believe that this patient was suffering from pyelonephritis because of the reduced concentration capacity and the elevated coli antibody titre.

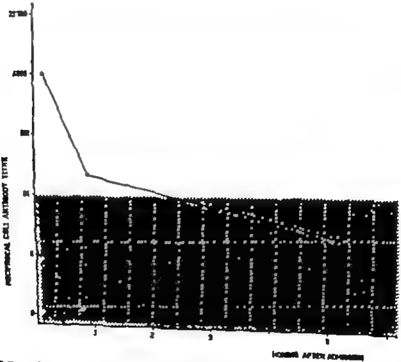

Fig. 6. Coli antibody titres in B. A., patient with asymptomatic bacteriuria, detected by a routine urinary culture.

SUMMARY

Earlier investigations have shown that the passive haemagglutination reaction is a specific and reliable tool in demonstrating humoral antibodies to different bacterial species.

In the first part of this survey some methodologic investigations are presented. It was found that the antibodies in the sera were partly or completely inactivated during storage at +4°C for about a month, while the activity was unchanged after at least six months at −20°C. The limiting concentration necessary for sensitization of the erythrocytes used in the reaction, was found to be around 60 million bacteria for different 0-antigens.

Four different sources of antigen were used during this investigation. Originally the infecting urinary bacteria from the patients were employed. Further studies compared this source with the faecal coli flora, with Kunin's common enterobacterial antigen and with a polyvalent antigen, consisting of a mixture of the eight *E. coli* 0-types most frequently encountered in urinary tract infections. The reason for these investigations were partly that some source other than urinary bacteria had to be used in the controls and in suspected cases of pyelonephritis without urinary excretion of bacteria, and partly that the preparation of individual antigens for each patient makes the method too complicated and time-consuming for use as a clinical routine procedure.

These studies revealed, that the faecal bacterial antigens gave results similar to the urinary ones in about half of the cases. The common enterobacterial antigen could not be used as a substitute for the homologous antigens since practically no antibodies were observed to this antigen in the sera. The polyvalent antigen was found to be a valuable substitute for the infecting strains, as equal titres could be demonstrated in those cases where the homologous urinary strains belonged to one or another of the types, included in the antigen pool. By means of this antigen it was also found that some patients, lacking antibody response to the bacterial strains, found in their urine, did have antibodies in elevated titres against the polyvalent antigen. This might be due to a continuous antigen stimulation from earlier infections. If this is proved, the finding indicates that determination of the coli antibody titre is a valuable tool in the detection of occult chronic pyelonephritis. However further studies are necessary to permit definite conclusions.

A material of controls was studied and it was found that almost all children above the age of about two months have agglutinating antibodies to *E. coli* in their serum.

A series of patients with uncomplicated first-time urinary tract infections with and without renal involvement were followed longitudinally. The findings showed that almost all of the patients above the age of three months with pyelonephritis had a sharp increase in the antibody titre, while those without functional impairment of the kidneys had titres within the limit of the control cases. It is thus possible to differentiate between cases of pyelonephritis and cases of lower urinary tract infections by means of this method. Elevated coli antibody titres were not

found in pyelonephritic patients below the age of two months. The reason for this is discussed.

A comparison between the antibody titre courses in patients with and without recurrences after their first episode revealed that the initial antibody response in the former group was not less than in the latter group

The rapid decrease (within 90 days) of the antibody titres found in most of the patients after treatment of the infections indicates that the homologous antigens were effectively eliminated by the treatment.

Determinations of the coli antibody titre were performed in some patients, whose clinical symptoms were suggestive of pyelonephritis, but in whom the usual urinary findings were absent or inconclusive. In eight out of thirteen of these a course of the antibody titre similar to that observed in patients with overt pyelonephritis was demonstrated and it is therefore regarded as most likely that these patients were in fact suffering from pyelonephritis.

Further the clinical use of antibody titrations in different types of urinary tract infections or their sequelae are illustrated by patients with recurrent urinary tract infection, renal hypertension and asymptomatic bacteriuria. The findings in some of these patients may indicate, that determination of antibodies to *E coli* is a useful instrument in the detection of some of those patients who are at risk for contracting chronic pyelonephritis.

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QUANTITATIVE STUDIES OF THE HUMAN NEONATAL CIRCULATION

A collection of articles

edited by

GÖRAN WALLGREN M.D

STOCKHOLM 1967

FOREWORD

Among the many unsolved problems in modern pediatrics, those pertaining to the neonatal cardio-pulmonary adaptation have been intensely studied during the last decade. It is undoubtedly correct that neonatal mortality to a great extent is made up of infants who do not manage to successfully accomplish this adaptation and a study of these adaptive mechanisms consequently represents major challenge in neonatal research.

Although our knowledge regarding the idiopatic respiratory distress syndrome in the newborn infant has been enriched in some respects our overall concept of the etiology and pathophysiology of the disease is still defective. The need for more basic information with respect to the adaptive capacity of the normal newborn, premature and full term, is obvious before we will be able to delineate the characteristic picture of the circulatory and respiratory handicap of the infant developing the respiratory distress syndrome.

A circulatory parameter that has attracted great deal of interest in this respect is placental transfusion. Does the additional blood received by the infant immediately after delivery of the body have any physiological implications? Does this transfusion, which may amount to 30 % or more of the infants total blood volume improve its capacity to succeed in the mature circulatory achievement associated with adaptation to extrauterine life? During the last few years these questions have been studied in a research program conducted in our hospital and many pieces of information have been brought together. These studies have shown that there are considerable differences in the circulatory and metabolic patterns between infants with and without this transfusion. The fact that clinically infants deprived of the placental transfusion seem to do just as well, has suggested an impressive adaptive capacity of the vascular system which has also been supported from studies during induced hypovolemia. Although the healthy normal infant seems to cope with decreased initial blood volume without adverse consequences for the outcome of the extrauterine adaptation, the possibility exists that the olemic state may affect the outcome of this adaptation in the newborn infant with impaired organ function.

It is clear from previous studies of the hemodynamic response to neonatal hypovolemia that an integrated concept of the circulatory pattern without actual blood flow determinations is impossible as the adaptive procedures reflect changes in the interacting parameters of flow and resistance. The following series of articles is devoted to studies designed to quantitate cardiac output in the newborn infant with subsequent pplication to hemodynamic

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Göran Wallgren

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From the Department of Pediatrics, Karolinska Hospital and the Southern Maternity Hospital, Stockholm, Sweden

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I. DYE DILUTION PRINCIPLES AND TECHNIQUES

JOHN S. HANSON, M.D.[1] RENÉ A. ARCILLA, M.D.[2]
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Indicator dilution techniques have won wide acceptance for a broad spectrum of cardiovascular clinical and research applications. Numerous communications have elaborated on the usefulness of this method for the estimation of cardiac output, as well as the detection and quantitation of intracardiac shunts and valvular defects. With very few exceptions these investigations were performed primarily on adult populations and, to some extent, on children above one year of age.

This report describes the various technical aspects involved in quantitative dye-dilution studies during the neonatal period. Methods, principles, instrumentation and calculations as adapted for use in this age group are presented, including an *in vivo* calibration technique, cardiac output estimation in the presence of left-to-right shunts, quantitation of arterio-venous (left-to-right) and veno-arterial (right-to-left) shunts and pulmonary blood volume. An integral factor implicit in such studies is employment of the so-called forward triangle method of dye curve analysis, and the following studies define a revised constant for such calculations in this particular age group.

Subjects, Procedure and Instrumentation

A total of 50 normal infants in the age range 2½—54½ hours forms the subject material for this and subsequent reports of newborn circulatory studies. The dye curves of 6 subjects without demonstrable shunt were utilized to derive a new forward triangle factor for cardiac output determination.

Following clinical examination of each infant, limb electrodes and a precordial microphone were applied for continuous electrocardiographic and phonocardiographic recording. The umbilical stump and surrounding skin were then thoroughly cleansed with PhisoHex® and Zephiran®. The umbilical stump was freshly cut, and two 5F infant feeding tubes 40 cm in length[1] were inserted into the umbilical vein and an umbilical artery. The venous catheter was advanced via the ductus venosus into the right atrium and subsequently through the foramen ovale into the left atrium. The arterial catheter was likewise advanced to a distance of 25—30 cm so that the tip lay approximately in the region of the aortic arch or root. (In 8 instances the catheter entered the pulmonary artery via the ductus arteriosus.)

The catheters were connected to EMT 35 strain gages,[2] and simultaneous recordings of pressure, electrocardiogram and phonocardiogram were made on the Mingograph 81 direct writing, 8-channel recorder.[2] Constant oscilloscopic monitoring of the electrocardiogram was conducted. Blood samples were analyzed for PO_2 using the Astrup Micro Equipment Model 22 with Clark oxygen electrode.[3] Radiologic methods were not employed in these infants. The catheter location was indicated by the distance of the catheter tip from the umbilical ring (compared with established anatomically-determined vascular distances (3)), the configuration of the pressure tracings, and the

[1] Sterilon Corporation, Buffalo, New York.

[2] Elema-Schönander, Stockholm, Sweden.

[3] Radiometer, Copenhagen, Denmark.

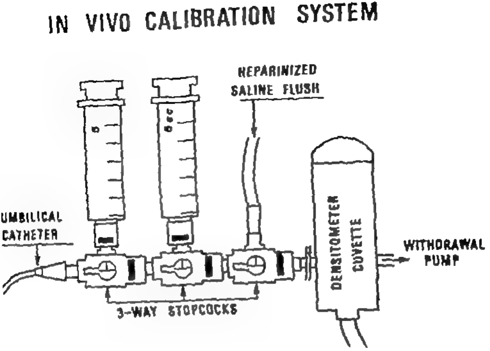

Fig. 1 Diagram illustrating sample arrangement for in vivo calibration of dye curves.

17 ml/min. A heparinized saline infusion system allowed flushing of the tubing and cuvette following reinfusion of blood to the infant upon completion of each dye curve. Saline remaining in the system was withdrawn by a separate syringe prior to the succeeding determination so that this added volume was not included in the withdrawal syringe and subsequently re-infused. Total dead space of venous and arterial catheters with connecting apparatus was 2.0 ml and was determined for each study. By virtue of this small dead space and use of a closed sterile system, blood loss was estimated to be less than 1.0 ml per curve recorded. A study comprising 20 curves, therefore, would result in slightly more than a 5 % blood volume reduction in a newborn infant over a period of 1—2 hours. Previous studies have shown (16) that even sudden volume depletions of this magnitude are well tolerated without extreme hemodynamic effects.

Due to the theoretical and practical objections to the use of placental blood obtained at delivery for dye-curve calibration, an *in vivo* method was developed which is both rapid and reliable. After all catheter connections had been made, the two 5 cc. syringes shown in Fig. 1 were filled with the infant's blood. Each syringe was in turn disconnected from its stopcock, air expelled, and the volume adjusted to exactly 5 cc. A Hamilton microsyringe of 50 µL capacity6 was used to dispense 25 and 50 µL of the 0.5 mg/ml. Cardio-green solution into the calibration syringes. The blood-dye mixtures were well agitated and the syringes reattached to the stopcocks. Since the plungers of the filled syringes were near the extreme

blood PO_2 values. The latter were particularly helpful in localizing the venous catheter at the left atrium or the arterial catheter at the pulmonary artery. In the final analysis, the contour as well as the appearance time of the arterial dye curves provided the best differentiation between left and right atrial catheter placement. Upon confirmation of the left atrial position of the catheter, the latter was secured by a purse-string suture to the umbilical stump.

A total of 140 normal newborns has been studied by umbilical catheterization in this facility according to the above procedure. In contrast to other reports (12), no febrile reactions, local or systemic infections occurred following these studies. One infant developed an umbilical hematoma which was noted to have resolved spontaneously at follow-up examination.

Dye-dilution Methodology

The umbilical catheter for injection of the indocyanine dye (Cardiogreen)[4] was attached by a system of 3-way stopcocks and Teflon tubing to a constant-volume injection syringe. Prior to the first dye curve, the catheter-stopcock-tubing system was filled with dye under positive pressure and the stopcock then closed until injection time. Failure to maintain positive pressure in the dye-filled catheter could result in retrograde displacement of dye, constituting a source of considerable error, particularly when injections are to be made into the arterial circuit. Despite this precaution, small amounts of dye will nevertheless be lost to the surrounding blood through capillary action and the effects of blood flow, and it thus is desirable to fill the catheter not more than 1 minute before intended injection. Estimation of this dye loss from an atrial catheter over a period of 3 minutes showed that approximately 3—5 % of the injected volume escaped from the catheter. Over a period of 1 minute, the loss of dye was insignificant.

Dye injection was accomplished manually by the operator who simultaneously pressed a signal button marking the recording. Flushing with saline was not done in this displacement method, a factor of importance in this age group for precisely timing the dye entrance into the circulatory system. An attempt was made to make the injection rate as uniform as possible to minimize variations on this basis. Similarly the operator, while watching the oscilloscopic electrocardiogram display, always tried to perform the injections at approximately the same point in the cardiac cycle during repeated determinations.

For the work under discussion, Cardiogreen in a concentration of 0.5 mg/ml was used, and an injection volume of 0.4 ml. This dosage of 0.2 mg dye per curve thus allowed registration of large numbers of curves without the risk of exceeding recommended limits of total dye administered.

The catheter employed for blood sampling, its tip usually situated in the proximal aorta, was connected by a series of 3-way stopcocks to the cuvette unit of a Waters X 301 densitometer[5] capable of background dye suppression up to a level of 36 mg/L. Response time for 67 % of final value with this instrument is 0.06 sec., and flow sensitivity is 97 % eliminated. The cuvette was in turn connected to a Sage-Waters constant speed infusion-withdrawal system which when fitted with a 20 cc. syringe withdrew sampling blood at a rate of 16—

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4 Hynson, Wescott & Dunning, Baltimore, Maryland

5 The Waters Corporation, Rochester, Minnesota

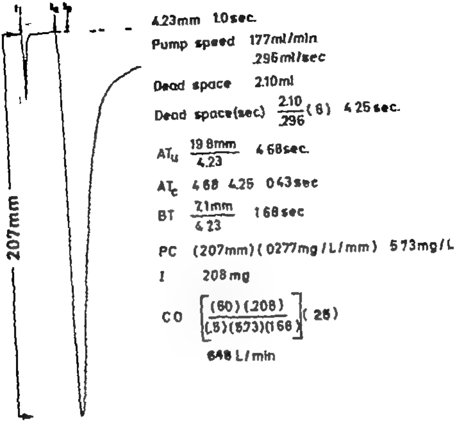


Fig. Dye curve calculations. AT_u = uncorrected appearance time. AT_c = corrected appearance time. BT = build-up time. PC = peak concentration. I = injectate. CO = cardiac output. t_i = injection time. t_a = appearance time. t_p = peak concentration time. The interval between two heavy time lines = 1 inch or 6 sec.

representing the functional dead space rather than the actual or anatomic dead space (15).

The original constant described for the forward triangle was 0.37 (7). Subsequent evaluation of the method (1) suggested that this should be revised to 0.34 in order to provide better correlation with the Hamilton method of total curve analysis. In both the original and later studies, the subject material was composed of adults, and many cases of acquired and congenital cardiac disease were included. In addition, the vast majority of dye curves was recorded following peripheral injection and/or sampling of dye.

It was with the constant 0.34 that we initiated our quantitative studies. After analysis of the recordings from several neonates, the suspicion arose that the forward triangle portion of these curves did not constitute 34 % of the total curve. It was felt that the factors of central injection and sampling, coupled with the very rapid circulation times, significantly altered this relationship. A relatively small ejection fraction (stroke volume/end-diastolic volume)

limit of their travel they could easily be removed despite the closed position of the stopcocks. Blood was then drawn through the densitometer from the infant for zero base line and subsequently from the two syringes to provide deflections corresponding to 2.5 and 5.0 mg/L. All blood was then re-infused. The system was originally planned to enable registration of 4 or more calibration points by simply repeating the procedure. However it was noted that the calibration factors corresponding to the 2.5 and 5.0 mg/L concentrations did not differ significantly in the same baby (error = 2.8 %, n = 25). Densitometer linearity was consistently established by this method, a result which we often had difficulties achieving when using placental blood.

With this means of calibration we have found that the calculated calibration factor varies considerably from infant to infant. In 25 consecutive calibrations the deflections corresponding to 5.0 mg/L varied between 162 and 198 mm, a range of 0.0254 to 0.0309 mg/L/mm for the constant. This represents a 20 % difference of the mean of these 25 values. This varies somewhat from previous reports (5) in which placental blood was used for densitometer standardization.

Calibrations and dye curves were recorded on a direct writing recorder[7] at a paper speed of 10 in./min. (4.23 mm/sec.) Paper width was 250 mm. The recorder was linear over the entire range of pen travel and 90 % response time for a full scale deflection was 0.■ sec. Depending on injection and sampling sites, peak concentration of dye curves varied between 130 and 220 mm or 3.8 to 6.5 mg/L at the recorder sensitivity employed.

[6] The Hamilton Company, Whittier, California

[7] E. H. Sargent & Company, Chicago, Illinois

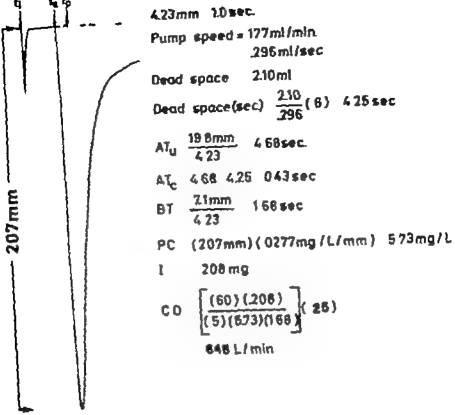
Quantitation of Dye Curves

Due to the very frequent presence of circulatory shunts in the early newborn period, evaluation of dye curves by the standard Hamilton method (9) is often impossible. Distortion of the primary curve along its exponential decay portion may occur very shortly after peak concentration has been attained due to the unusually rapid circulation time. Logarithmic extrapolation of the downslope is therefore obviated.

In order to overcome such difficulties which are also inherent in curves from patients with valvular regurgitation or cardiac decompensation, Hetzel et al. (7) investigated the possibility of evaluating any dye curve through its initial portion up to the point of peak concentration. This forward triangle method has since found wide application for estimation of cardiac output, not only from "problem" curves, but also as a relatively easy and time-saving method in itself. The derived values for cardiac output so obtained and the associated range of variability are generally considered to validate the method. The basic formula employs values for the time from curve appearance to peak concentration (build-up time, BT), the peak concentration itself (PC), the amount of injected dye (I) and a factor K, determined by the authors. The relationship of these factors is expressed by

$$\text{Cardiac output} = \frac{60\ I}{0.5\ (PC)\ (BT)} \times K$$

A sample calculation with the derivation of necessary values is given in Fig. 2. The factor of 0.6 appearing in the formula for dead space in this Figure is a correction factor relating the parabolic distribution of dye particles in the moving column of blood along the catheter-cuvette tubing assembly.



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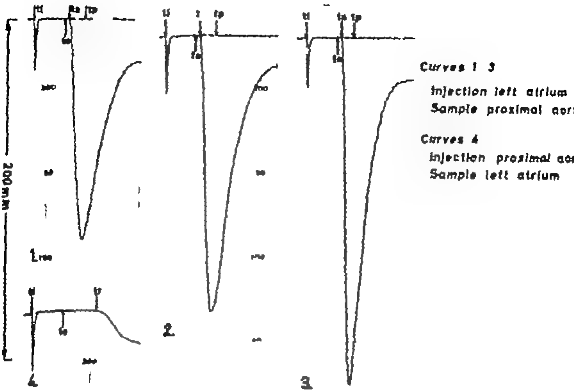


Fig 3 Series of 3 dye curves resulting from left atrial injection and a fourth ... from aortic injection and left atrial sampling Curve 4 indicates absence of left-to-right ductal shunt Variation in cardiac output of curves 1—3 is secondary to hemodynamic changes intentionally induced during study Symbols as in Fig

in neonates could also be an important consideration in this regard

To clarify this problem, a total of 55 dye curves was recorded following left atrial injection and proximal aortic sampling in 6 infants aged 27 to 54 hours (mean 44 4 hours) All curves contained a minimum of 4 points on the exponential decay segment prior to onset of re-circulation which were in linear relationship when plotted logarithmically Many exhibited 5—6 such points. Absence of left-to-right ductus arteriosus shunt was attested to by the lack of a densitometer response prior to recirculation after injection in the proximal aorta and sampling in the left atrium (see Curve 4 Fig 3) This is in conformity with the studies of Moss et al (11) in which a ductal shunt was usually no longer demonstrable by blood gas analysis after 15 hours of age in normal term infants. It is possible however that a small L R shunt through the foramen ovale may occur if the left atrial catheter displaces the foramen valve Such a small shunt, which might not produce an obvious recirculation peak on the primary curve would also not be detected by aortic injection with left atrial sampling There does not appear to be a convenient method for detecting such a hidden shunt short of left atrial injection with right atrial sampling, and the possible presence of this

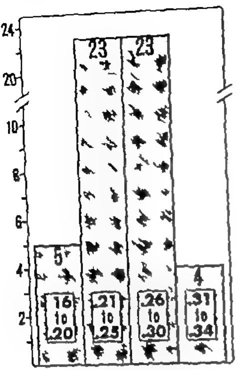


Fig. 4 Frequency distribution of forward triangle factor K, calculated from dye curves with left atrial injection and proximal aortic sampling in normal newborn infants.

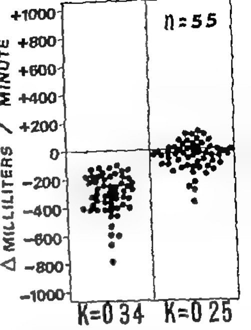


Fig. 5 Frequency distribution of differences in cardiac output calculated by Hamilton re-plot method and forward triangle method using factors 0.34 and 0.25 for the latter. Mean difference for 0.34 factor is −0.311 L/min. and for the 0.25 factor is −0.051 L/min.

catheter-induced artifact, therefore, represents an inherent but probably minor imperfection of the dye-dilution method.

The mean value of the forward triangle area relative to total curve area was 0.25 ± 0.005 S.E. for the left-atrial injection studies. This represents a 24% reduction of the 0.34 figure developed in adults. Frequency distribution of the individual constants calculated is represented in Fig. 4. When the 55 left-atrial curves were recalculated with the new factor of 0.25 instead of 0.34, the mean difference between cardiac output determined by the Hamilton and by the forward triangle methods decreased from −0.311 L/min. to −0.051 L/min. This is presented graphically in Fig. 5. Despite the obviously much-improved correlation of output values derived by the two methods when employing the 0.25 forward triangle factor, it is apparent that isolated instances of wide divergence still exist. This limits the reliance which may be placed on a single determination, and indicates that duplicate or even triplicate curve recordings should be carried out when feasible.

The reproducibility of cardiac output estimation by this method is surprisingly good (6, 13) particularly when determinations are performed with only 2—3 minutes delay between individual curves. This is illustrated in Fig. 6 and Fig. 7 for curves

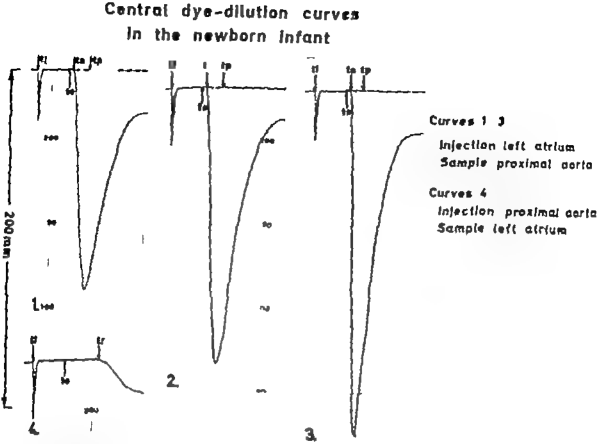


Fig 3 Series of 3 dye curves resulting from left atrial injection and a fourth curve from aortic injection and left atrial sampling. Curve 4 indicates absence of left-to-right ductal shunt. Variation in cardiac output of curves 1—3 is secondary to hemodynamic changes intentionally induced during study. Symbols as in Fig 2

in neonates could also be an important consideration in this regard.

To clarify this problem, a total of 55 dye curves was recorded following left atrial injection and proximal aortic sampling in 6 infants aged 22 to 54 hours (mean 44.4 hours). All curves contained a minimum of 4 points on the exponential decay segment prior to onset of re-circulation which were in linear relationship when plotted logarithmically. Many exhibited 5—6 such points. Absence of left-to-right ductus arteriosus shunt was attested to by the lack of a densitometer response prior to recirculation after injection in the proximal aorta and sampling in the left atrium (see Curve 4 Fig 3). This is in conformity with the studies of Moss et al (11) in which a ductal shunt was usually no longer demonstrable by blood gas analysis after 15 hours of age in normal term infants. It is possible, however, that a small L-R shunt through the foramen ovale may occur if the left atrial catheter displaces the foramen valve. Such a small shunt, which might not produce an obvious recirculation peak on the primary curve, would also not be detected by aortic injection with left atrial sampling. There does not appear to be a convenient method for detecting such a "hidden" shunt short of left atrial injection with right atrial sampling, and the possible presence of this

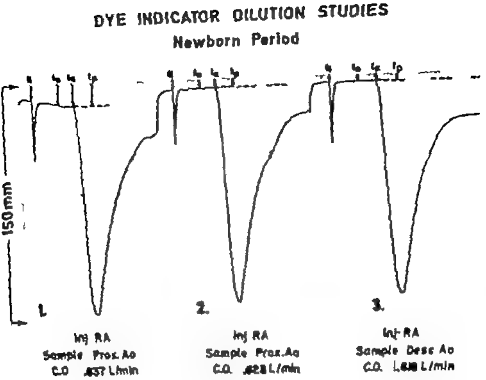
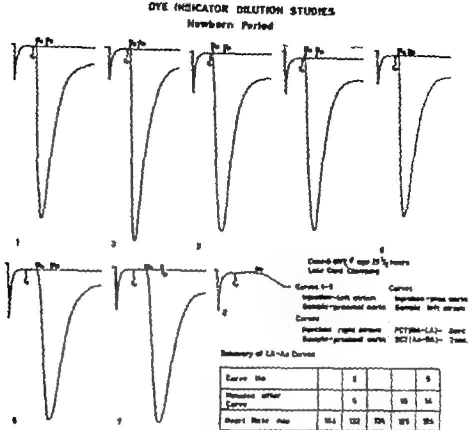


Fig. Three consecutive right-atrial-injection curves made at 2-minute intervals to demonstrate reproducibility of the method for cardiac output estimation.

ber the shunt will appear on the decay portion of the curve (Curve 1 Fig 8)

Calculation of left-to-right shunt employs an extension of the forward triangle method and is based on the assumption that the area under the peak of the shunt curve is inversely proportional to shunt flow while the area under the primary peak is inversely proportional to right ventricular output. Several factors must be extracted from the curve for this calculation, namely appearance and build-up times of the shunt and primary curves, and peak concentrations of both curves. In addition, the pulmonary circulation time must be known to enable derivation of the build-up time of the shunt curv

Pulmonary circulation time (PCT) is reflected in the difference in the appearance times of the curves following right atrial (or right ventricular) injection and left atrial injection using the same arterial sampling site. Change of the catheter injection sites should be as rapid as possible to minimize errors from an unsteady state. In the presence of a left-to-right ductal shunt, dye injection in the aortic root and left atrial sampling also indicates the PCT the appearance time of the dye curve representing the shortest traversal time of the dye across the aorta, ductus, pulmonary vascular bed and left atrium. Similarly if the aortic catheter has entered the pulmonary artery through the ductus, injection may be made



Curve No		[illegible]			[illegible]
Minutes after Curve		[illegible]		[illegible]	[illegible]
Heart Rate /min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Appearance Time (sec)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pulmonary Blood Flow L/min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
L/min	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Stroke Output (ml)	[illegible]		[illegible]	[illegible]	[illegible]

Fig 6 Central dye-dilution curves demonstrating reproducibility of method. t_i = injection time t_a = corrected appearance time t_u = uncorrected appearance time t_p = peak concentration time t_r = recirculation time

derived from left and right atrial injections, respectively The close agreement of values for pulmonary blood flow in curves 1 2 3 and 3 4 of Fig 6 (representing two sets of physiological conditions) and of all three curves of Fig 7 is apparent. It is, of course, necessary to pay strict attention not only to the quiescent state of the infant but also to the rapid variation in heart rate when comparing flow estimations, and simultaneous recording of electrocardiogram and dye curves is essential for intelligent interpretation of results.

Shunt Estimation

In common with recently published reports (10) we have made use of a modification of a method suggested by Swan et al. (14) for left-to-right extra-cardiac shunt quantitation Since the pulmonary circulation time in the newborn is characteristically very rapid, it is impossible to make use of dye curves from right-atrial injections because the shunt will appear mixed in the primary curve before peak concentration is reached For this reason, ductal shunt may be calculated only after left-atrial injection

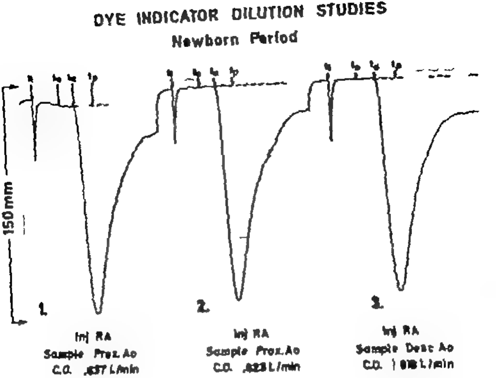


Fig. 7. Three consecutive right-atrial-injection curves made at [illegible]-minute intervals to demonstrate reproducibility of the method for cardiac output estimation.

where the shunt will appear on the decay portion of the curve (Curve 1 Fig. 8).

Calculation of left-to-right shunt employs an extension of the forward triangle method and is based on the assumption that the area under the peak of the shunt curve is inversely proportional to shunt flow while the area under the primary peak is inversely proportional to right ventricular output. Several factors must be extracted from the curve for this calculation, namely appearance and build-up times of the shunt and primary curves, and peak concentrations of both curves. In addition, the pulmonary circulation time must be known to enable derivation of the build-up time of the shunt curve.

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DYE INDICATOR DILUTION STUDIES

Newborn Period

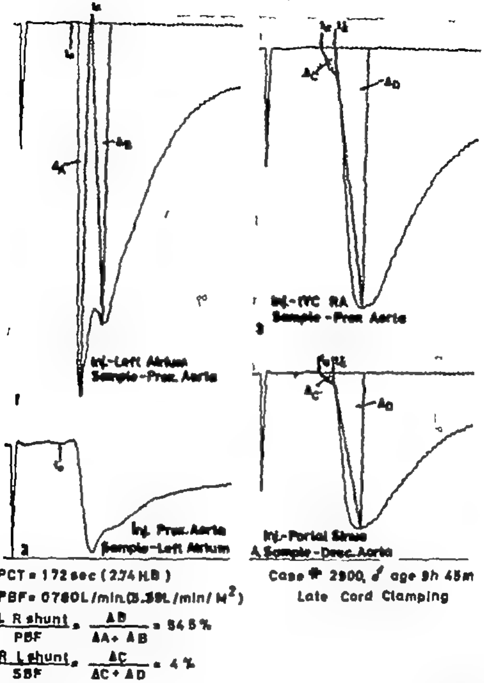

Fig. 8. Dye curves recorded from various injection and sampling sites exhibiting left-to-right and right-to-left shunt and method of shunt calculation. t_o = corrected appearance time. t_a = L R shunt appearance time. t_a = R L shunt appearance time. t_j = appearance time of primary curve. H.B = heart beats.

at the former site and sampling performed in the left atrium. A comparison of the PCT's obtained by the first two methods was made in 12 infants. A mean value and standard error of 2.01 ± 0.05 sec. was obtained for the PCT derived from the combined *right* and *left-atrial* injection curves, while corresponding figures for aortic injection with *left-atrial* sampling were 1.85 ± 0.11 sec. ($r = 0.63$). Obviously PCT must be established for each individual rather than attempting to apply a mean value.

Once the estimation of PCT has been made, the remaining factors necessary for the shunt formula are easily obtained. With reference to Curve 1 Fig. 8, the time of shunt appearance, t_a, is located as the difference between the peak concentration time of the shunt and PCT. Build-up time of the shunt and primary curves are then measured as are their peak concentrations. The latter may be expressed, with linear densitometer response, in millimeters of deflection without conversion to corresponding mg/L concentration, since the calibration factor mg/L/mm cancels out in the formula where shunt is expressed as a fraction of total pulmonary blood flow (PBF)

$$\frac{\text{L-R shunt}}{\text{PBF}} = \frac{(BT_s)\ (PC_s)}{(PC_1)\ (BT_1) + (BT_s)\ (PC_s)}$$

or referring to Fig. 8 again

$$\therefore \text{L-R shunt} \approx \frac{\text{area B}}{\text{area A} + \text{area B}}$$

Theoretically it may be stated that this method of shunt estimation is not entirely valid because the shunt curve's peak concentration, PC_s, actually represents a summation effect of primary curve and shunt curve, not the shunt curve effect alone. This consideration is diagrammed in Fig. 9 to illustrate that PC_s is actually the height to which the primary curve's decay portion is deflected by the peak concentration of a simultaneously-occurring curve due solely to true shunt. The finding that the magnitude of a L-R shunt can be estimated fairly accurately (10) by the equation above is probably due to area B's appearance in both numerator and denominator and the frequent appearance of shunt effect relatively low on the rapidly falling primary curve, thus tending to minimize the difference between *true* shunt curve PC and that measured for use in the formula. Were it possible to establish the primary curve exponential decay, true shunt PC could then be measured (dimension X, Fig. 9), but this is usually impossible.

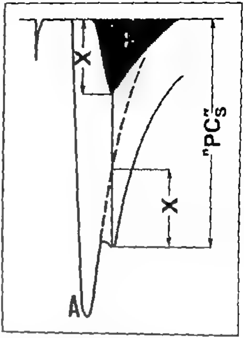

Fig. 9. Illustrating that actual shunt curve B (cross-hatched area) displaces primary curve A decay portion (dashed line) by height X. Dimension PC_s, therefore, does not represent actual peak concentration of shunt but its effect on the primary curve. Recirculation is not depicted.

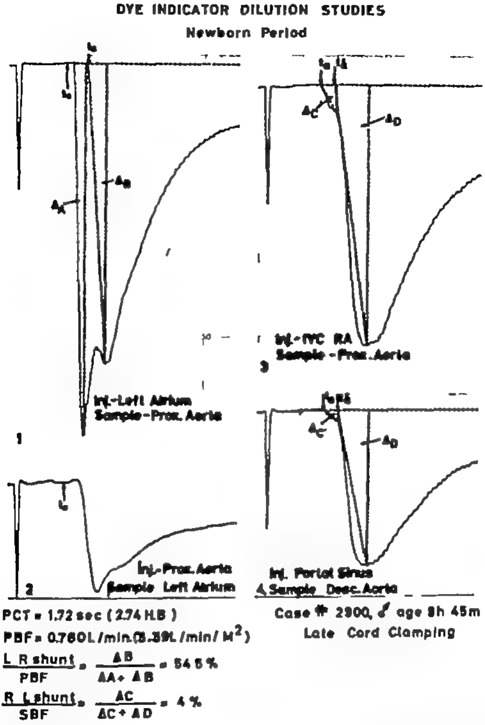

Fig 8 Dye curves recorded from arious jection nd sampling sites exhibiting left-to-right and right-to-left shunt and method of shunt calculation. t_a = corrected appearance time t_s = L R shunt ppearance time t_s = R L shunt appearance time t_i = ppearance time f primary curv H B = heart beats.

triangle is but one example of this. An analogous situation occurred with regard to shunt calculations by Carter's formulae (2) where it was found that significant over estimation of shunt existed by virtue of extremely early appearance of ductal flow in the dye curve.

SUMMARY

Principles and techniques for the application of indicator-dilution studies to the newborn period are discussed. A simple method for *in* [illegible] dye curve calibration is described, and a modification of the forward triangle factor for cardiac output estimation in this age group is presented. Methods of calculation of cardiac output and shunts are given. Many problems unique to the neonatal period are suited to study by careful application of these techniques.

ACKNOWLEDGEMENT

The authors wish to express their appreciation of the invaluable technical assistance given by Mrs. Ulla Führer, Mrs. Ingrid Werner and Mrs. Signe Bergströmer

Another theoretic consideration limiting the reliability of shunt estimation by this method concerns the validity of applying a primary curve forward triangle factor of 0 25 to the shunt curve Almost certainly differences in circulation transit times produce a shunt curve forward triangle area which represents more than 25 % of the total curve. This undoubtedly introduces some error into the shunt quantitation method outlined above. Nevertheless, as has been demonstrated despite these inconsistencies, meaningful evaluation of shunt magnitude can be accomplished (10) by means of the simple dye-curve measurements described

The magnitude of right to-left shunting is evaluated in a similar manner (Curve 2 Fig. 8) Appearance time of the primary curve, t_{a} is estimated from the PCT and the areas of shunt and primary curves are obtained as above

In dye-dilution curves with ductus arteriosus left to-right shunt only and no other intracardiac shunt PBF equals left ventricular output (LVO) Since the ductal shunt is expressed as a fraction of PBF right ventricular output (RVO) is derived according to the following relationships as modified from Gessner et al (5)

$$PBF = RVO + L\ R \text{ shunt}$$

$$PBF = RVO + \frac{(\%\ L\ R)}{100}\ (PBF)$$

$$RVO = PBF - \frac{(\%\ L\ R)}{100}\ (PBF)$$

Since $LVO = PBF$

$$RVO = LVO - \frac{(\%\ L\ R)}{100}\ (LVO) =$$

ESBF (effective systemic blood flow)

Miscellaneous Calculations of Interest

Systemic circulation time may be derived from the aorta to-left atrium curves The PCT derived as previously discussed, is then subtracted from the aorta to-left atrium circulation time.

An approximation of pulmonary blood volume may be made using the parameters of PBF PCT injected amount of dye and peak concentration of the dye curve following pulmonary artery injection with left atrial sampling These factors are related by the expression (8)

$$PBV = \frac{(PBF)\ (PCT)}{60} + \frac{I}{PC}$$

DISCUSSION

The recent interest accorded the human organism's adaptation to extra-uterine life has far-reaching consequences. Studies centered on the neonatal period are of great importance not only for the establishment of normal values but also as the basis for investigating disease states and devising therapeutic programs. Examples of such applications may be found in answering questions relative to early versus late umbilical cord clamping and study of the respiratory distress syndrome The newborn infant can by no means be considered a micro version of the adult, and consequently mere miniaturization or direct transference of examination techniques valid for the adult may not pertain.

These considerations have been substantiated repeatedly during the performance of indicator-dilution studies in newborn infants. Extremely rapid circulation times and the frequent presence of shunts have required alteration of previously accepted methods. The modification of the forward

triangle is but one example of this. An analogous situation occurred with regard to shunt calculations by Carter's formulae (2) where it was found that significant over estimation of shunt existed by virtue of extremely early appearance of ductal flow in the dye curve.

SUMMARY

Principles and techniques for the application of indicator-dilution studies in the newborn period are discussed. A simple method for [illegible] dye curve calibration is described, and a modification of the forward triangle factor for cardiac output estimation in this age group is presented. Methods of calculation of cardiac output and shunts are given. Many problems unique to the neonatal period are suited to study by careful application of these techniques.

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QUANTITATIVE STUDIES OF THE HUMAN NEONATAL CIRCULATION

II. HEMODYNAMIC FINDINGS IN EARLY AND LATE CLAMPING OF THE UMBILICAL CORD

by

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Supported by an Advanced Research Fellowship of the American Heart Association and the Heart Association of Palm Beach and Martin Counties, Florida; Assistant Professor of Pediatrics, University of Florida, Gainesville, Florida.

Supported by the Association for the Aid of Crippled Children, New York, New York, the Swedish National Association against Heart and Chest Diseases, and by USPHS Grant No. 1 M01 FR-00305-01 — Pediatrics Multicategorical Clinical Center No. 1

Interest in the circulatory dynamics of the newly born infant has increased in recent years. Cardiac catheterization, chiefly intracardiac pressure measurements and blood gas analyses, have been performed during the first hours or days of life (1 3, 8, 20 21). However cardiac output, shunt flow quantitation, and vascular resistance have generally not been determined due to technical difficulties.

The cardiovascular status of the neonate (9 18) has also been evaluated by the dye indicator dilution technic. Recent studies show that in the neonate with left-to-right shunt, peripheral venous or even right heart dye injection is not reliable for cardiac output estimation because of the very rapid pulmonary circulation time (9 13).

This communication presents the results of two-catheter dye dilution studies in 11 newborn infants with early clamping of the umbilical cord and in 36 infants with delayed clamping of the cord. Previous studies (17 26) have established significant differences in the blood volumes of these two groups, presumably related to the magnitude of placental transfusion. This investigation was initiated to determine the influence of perinatal placental blood transfer on the cardiovascular adjustments after birth.

MATERIAL AND METHODS

Forty-seven normal, term, newborn infants were studied by cardiac catheterization and dye indicator dilution technic. The subjects were classified into two groups according to the time at which the umbilical cord was clamped (1) *early* clamp group (EC) where the cord was clamped within 2 to 10 seconds after delivery of the trunk and, (2) *late* clamp group (LC) where the cord was clamped after cessation of the umbilical artery pulsations, generally 3 to 5 minutes after birth.

The EC group comprised 11 infants 2¾ to 12½ hours old at the time of the indicator dilution study. There were 7 males and 4 females with a mean birthweight of 3 39 kg (range 2.68 to 3.80 kg). The LC group comprised 36 infants 2½ to 54 hours of age. There were 20 males and 16 females. Their mean birthweight was 3 70 kg (range 3.04 to 4.87 kg). The difference in the mean birthweights was significant ($P<0.02$)

All subjects were products of uneventful pregnancies. Delivery was uncomplicated and through the vaginal route in cephalic presentation. Pethidine in dosages of 50 to 150 mg was administered intramuscularly to 6 mothers (2, EC group 4, LC group) several hours before delivery. Nitrous oxide was administered intermittently to 15 mothers (6 EC group 9 LC group). All infants cried spontaneously after birth, and none required resuscitation. No cardiopulmonary abnormality was observed clinically. With the exception of 14 LS infants over 14 hours of age, all infants were studied prior to their first feeding. No anesthesia, antibiotics, or other medication was employed. Room temperature was 25°C to 26°C, and all subjects breathed room air. No complications related to the procedure occurred aside from a mild umbilical stump

hematoma in one subject which resolved spontaneously

Cardiac catheterization was performed by the transumbilical approach A 5-F soft polyvinyl catheter[1] with two side holes 6 mm apart near its tip was inserted into the umbilical vein, and another into an umbilical artery They were gently advanced centrally into the cardiac chambers without fluroscopic guidance. Intracardiac and vascular pressures were recorded and blood samples obtained for gas analysis Catheter position was indicated by the distance of the tip from the umbilical ring, the pressure curve, the blood gas findings, and the configuration and appearance time of the dye curves Upon establishment of the desired intracardiac position of the catheter the latter was secured by a purse-string suture to the umbilical stump The technic has been described previously (3)

A three way stopcock connected the injection catheter to a 10 ml reservoir syringe containing 0 5 mg/ml dye solution (Cardiogreen®)[2] and to a 2 ml syringe adjusted to deliver a constant volume of 0 4 ml Immediately preceding each injection, the catheter and delivery syringe were filled under positive pressure from the 10-ml reservoir Special care was taken to eliminate air bubbles. The dye thus delivered by volume displacement, was injected manually the operator simultaneously pressed a signal button to record the instant of injection.

The sampling catheter was connected to the cuvette unit of a Waters X 301 densitometer with a Teflon tubing The volume of this catheter to-cuvette assembly ranged from 1 5 to 2 0 ml. During the inscription of the dye curve, blood was withdrawn with a Sage Waters withdrawal infusion pump into a 20-ml lubricated heparinized syringe at a rate of 16 to 17 ml/min. It was re infused into the baby immediately afterward A Sargent direct writer recorded galvanometer deflections at a paper speed of 10 in/min. (4 23 mm/sec.) Response time for 90 % of full scale deflection was 0 9 second Densitometer and recorder response was linear in the range of dye concentrations used and over the entire range of pen travel

The appearance time was corrected for catheter delay time (25) (see Appendix I) In the first 16 cases cord blood in three dye concentration ranges was used for calibration. In the subsequent cases, an *in vivo* calibration method was used prior to the actual dye curve studies (11) Two 5-ml samples of the baby s blood were withdrawn into heparinized syringes 25 and 50 µL of dye solution were added with a Hamilton microsyringe to yield a concentration of 2.5 and 5 0 mg/L, respectively The syringes were connected in series to the arterial catheter by two three-way stopcocks. Blood was drawn from the infant to establish the zero baseline and subsequently from each syringe (with plunger removed) All blood was then immediately re infused The calibration factor converted recorded deflection in millimeters into dye concentration in milligram per liter of blood

Cardiac output and left to-right shunts were determined by injection into the left atrium and sampling from the aorta proximal to the ductus arteriosus In 4 cases, sampling was from the descending aorta alone. In 8 infants, the injection and sampling sites were the pulmonary artery and left atrium, respectively Right to-left atrial shunting was determined by injecting the dye into the right atrium and sampling from the proximal aorta. The procedure was re

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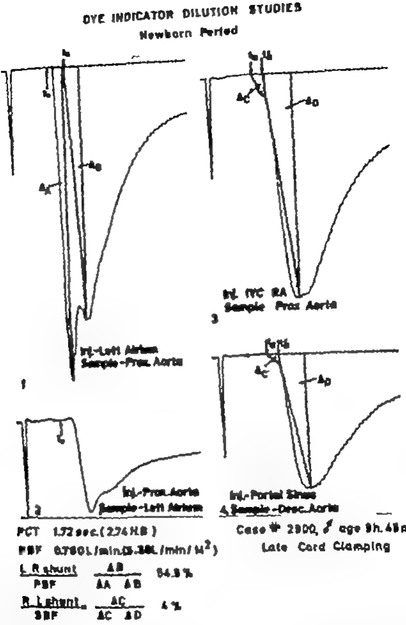

F 1 Dy dilution curves of a 9-¾-hour old male LC infant ith bidirectional shunts. The pA LA curv (No 2) onfirms the ductal (arteriovenous) shunt and show PCT of 1 72 seconds. estimated left-to-right shunt ($\frac{\Delta B}{\Delta A+\Delta B}$) as 54 5 of pulmonary blood flow the estimated to lef shunt ($\frac{\Delta C}{\Delta D+\Delta C}$) as 4 % of systemic flow Pulmonary blood flow as 3 39 L/m/M²

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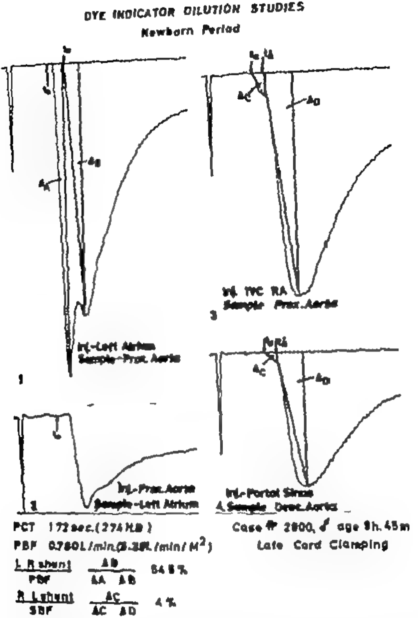

F 1 Dye dilution curves of 9-¾-hour old male LC infant with bidirectional shunts. The pAo → LA run (No. 2) confirms the ductal (arteriosus) shunt and shows PCT of 1.72 seconds. The estimated left-to-right shunt ($\frac{\Delta B}{\Delta A+\Delta B}$) was 54.5% of pulmonary blood flow; the estimated right-to-left shunt ($\frac{\Delta C}{\Delta D+\Delta C}$) was 4% of systemic flow. Pulmonary blood flow was 3.39 L/m/M²

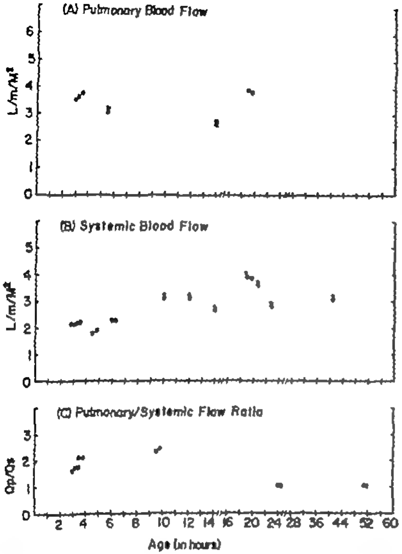

Fig Scattergram of the pulmonary blood flow index systemic blood flow index, and pulmonary systemic flow ratio in the two groups of subjects plotted against age. Circles with crosses belong to the cases where the tiny left-to-right shunt was ignored and the systemic flow assumed to equal pulmonary flow

Solids = EC infants.
Circles = LC infants

peated using the descending aorta as the sampling site for detection of ductal (or combined ductal and atrial) right-to-left shunting In the cases showing a shunt by the latter technic, right ventricular injection to confirm the ductal origin of the shunt was not done due to failure to advance the venous catheter into the right ventricle

Cardiac output was calculated by the forward triangle method (5 12) with some modification (see Appendix II) The estimated output value of each case represented the average of 2 to 6 or more, dye curves. In 6 LC infants aged 22 to 54 hours (mean 44 4 hours) without demonstrable shunt, a total of 35 left atrial-to-proximal aortic (LA → pAo) dye curves was obtained to derive the K factor for the forward triangle method.

A left-to-right shunt was indicated by a secondary deflection appearing early in the disappearance slope of the curve and separate from that of the recirculation curve (fig 1) The origin of this shunt from a patent ductus arteriosus was confirmed by reversing the injection and sampling sites i e by injecting the dye into the aorta pro

DYE INDICATOR DILUTION STUDIES

Newborn Period

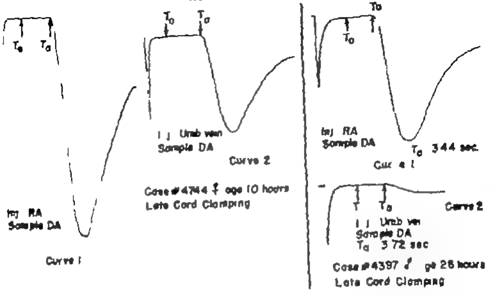

Fig. Dye dilution curves of 2 LC infants, demonstrating functional patency of the ductus arteriosus of varying degree. Curve 2 of the 10-hour-old infant is grossly similar to that of Curve 1 except for its height, whereas Curve 2 of the 26-hour-old infant consists only of a tiny deflection.

arterial in the ductus and sampling from the left atrium. Quantitation of the left-to-right shunt was made from the LA → pAo and from the pulmonary artery-to-left atrial (PA → LA) dye curves (see Appendix III). Systemic blood flow was also estimated, and the corresponding pulmonary/systemic flow ratio was derived (fig. 2). Pulmonary and systemic vascular resistances were also computed using the standard formula

$$\text{Pulmonary P.R.U.} = \frac{PA_m - LA_m \text{ (in mm Hg)}}{Q_p \text{ (per M}^2\text{ of B.S.A.)}}$$

$$\text{Systemic P.R.U.} = \frac{Ao_m - RA_m \text{ (in mm Hg)}}{Q_s \text{ (per M}^2\text{ B.S.A.)}}$$

A right-to-left shunt was indicated by an abnormally short appearance time and an early hump in the build-up slope of the right atrial-to-aortic dye curve (Fig. 1). The size of the shunt was estimated by Swan's method (23), but the theoretical appearance time of the primary curve was estimated from the pulmonary circulation time (see Appendix IV).

The pulmonary circulation time (PCT) was indicated by the appearance time of the PA → LA dye curves. In neonates with left-to-right ductal shunts, the appearance time of the pAo → LA dye curves also yielded the PCT since the shunt pathway consisted of the ductus and pulmonary vascular bed. The PCT was also indirectly indicated by the difference in the appearance times of the right and left-atrial injection dye curves using the same aortic sampling site. The latter values actually measured the right atrium-to-left atrium circulation time.

Table 1 Summary of Hemodynamic Data in EC and LC Newborn Infants[1]

Parameters	—6 Hours			>6—12 Hours			>1 — 3 Hours		3—51 Hours
	EC	LC	t-test	EC	LC	t-test	EC	LC	LC
Heart Rate (beats/mm)	n=6 127 ±3 6	n=9 113 ±3 3		n=4 117 ±1 2	n=10 107 ±4 2		n=1 121	n=6 122 ±5 5	n=10 124 ±4 8
Left Ventricular Stroke Volume (ml)	n=6 6.9 ±1 14	n=7 6 3 ±0 50	P>0 6	n=4 6 3 ±0 36	n=10 8 1 ±0 40	P>0 01 <0 02	n=1 4 7	n=6 6 8 ±0 93	n=10 6.5 ±0 44
Left Ventricular Output[2] L/min/M[2]	n=6 3 87 ±0 404	n=8 3 07 ±0 247	P>0 15 <0 10	n=4 3 14 ±0 130	n=10 3 66 ±0 58	P>0 2	n=1 2 52	n=6 3 25 ±0 266	n=10 3 48 ±0 ?66
Right Ventricular Output[3] L/min/M[2]	n=6 2 11 ±0 256	n=6 1 93 ±0 072	P>0 5	n=3 2 22 ±0 434	n=9 1 98 ±0 152	P>0 5	n=1 2 52	n=2 2.63 ±1 014	n=9 3 54 ±0 238
Systemic Vascular Resistance (P R.U)	n=6 26 6 ±2 32	n=6 30 6 ±4 61	P>0 4	n=3 25 2 ±0 57	n=8 30 1 ±. 34	P>0 3	n=1 21	n=2 25 5 ±11 13	n=8 19 6 ±2 32
L R Shunt*	P=6 A=0	P=10 A=0	X^2=0	P=1 A=3	P=10 A=0	X^2=2 69 P=0 10	P=0 A=1	P=5 A=1	P=1 A=9
R L Shunt*	P=1 A=5	P=1 A=8	X^2=0 288 P<0 70	P=0 A=5	P=4 A=6	X^2=2 24 P>0 10	P=0 A=1	P=0 A=6	P=0 A=10

[1] Values ndc t Mean±1 S E
Eq f nt t pulmonary blood flow
Eq f nt t d blood flow

P=present A=absent
n=number

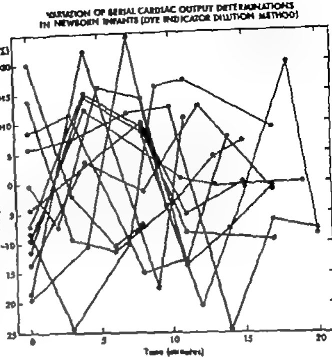

Fig 4 Serial cardiac output determinations of newborn infants at rapid intervals. Each dot represents the per cent difference of single output from the mean of the respective series 0 minute refers to the first determination

Functional patency of the ductus venosus was investigated by umbilical venous injection and subsequent right atrial injection. A constant sampling site consisting of either the pulmonary artery or the aorta was used (fig 3)

RESULTS

The reproducibility of the dye curves is illustrated in figure 4, where the individual cardiac output values have been plotted as percent difference from the mean output of each series One standard deviation of the percentile variation about the mean was ±11.75%

The indirect PCT derived from the RA and LA injection curves showed fair correlation with that obtained by the corresponding pAo → LA and PA → LA curves ($r = +0.63$) The average PCT for all subjects was 1.86 seconds ±0.46 S.D (range 0.9 to 2.4 seconds) 1 There was no appreciable difference between the early and the late age groups, or between the EC and LC subjects. Pulmonary circulation time was also converted into heart beats by the equation

$$H.B = PCT \times \frac{\text{heart rate/min.}}{60}$$

This averaged 3.59 heart beats ±0.925 S.D with a range of 1.65 to 5.0 heart beats (fig 5)

Table 1 is a summary of the heart rate, left ventricular stroke volume, left ventricular output (numerically equivalent to

The PCT derived from the RA and LA injection curves was utilized only in those without sharp onset of the PA → LA or pAo → LA curves. None had right-to-left shunts.

Table 1 Summary of Hemodynamic Data in EC and LC Newborn Infants1

Parameters	—6 H urs			>6—12 Hours			>1 —25 Hours		5—51 Hours
	EC	LC	t-test	EC	LC	t test	EC	LC	LC
Heart Rate (beats/min)	n=6 127 ±5 6	n=9 113 ±5 3		n=4 117 ±1 2	n=10 107 ±4 2		n=1 121	n=6 122 ±5 5	n=10 124 ±4 8
Left Ventricular Stroke Volume (ml)	n=6 6.9 ±1 14	n=7 6.3 ±0 50	P>0 6	n=4 6 3 ±0 36	n=10 8 1 ±0 40	P>0 01 <0 02	n=1 4 7	n=6 6 8 ±0 93	n=10 6.5 ±0 44
Left Ventricular Output2 L/min/M2	n=6 3 87 ±0 404	n=8 3 07 ±0 247	P>0 15 <0 10	n=4 3 14 ±0 130	n=10 3 66 ±0 258	P>0 2	n=1 2 52	n=6 3 25 ±0 266	n=10 3 48 ±0 266
Right Ventricular Output3 L/min/M2	n=6 2 11 ±0 256	n=6 1 93 ±0 072	P>0 5	n=3 2 22 ±0 434	n=9 1 98 ±0 152	P>0 5	n=1 2 52	n=2 2 63 ±1 014	n=9 3 54 ±0 238
Systemic Vascular Resistance (P.R.U.)	n=6 26 6 ±2 32	n=6 30 6 ±4 61	P>0 4	n=3 25 2 ±0 57	n=8 30 1 ±2 34	P>0 3	n=1 21	n=2 25 5 ±11 13	n=8 19 6 ±2 32
L R Shunt*	P=6 A=0	P=10 A=0	X2=0	P=1 A=3	P=10 A=0	X2=2 69 P=0 10	P=0 A=1	P=5 A=1	P=1 A=9
R L Shunt*	P=1 A=5	P=1 A=8	X2=0 288 P<0 70	P=0 A=5	P=4 A=6	X2=2 21 P>0 10	P=0 A=1	P=0 A=6	P=0 A=10

1 Values indicate Mean ± 1 S E
Fq lent t pulmonary blood fl w
I qu k nt t nts in blood flow

P=present A=absent
n=number

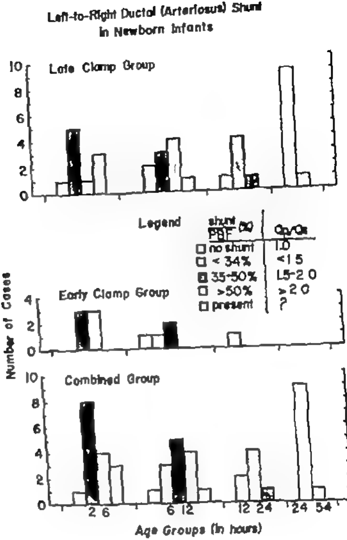

Fig 6 Relative frequency of left-to-right shunts in the newborn period.

Of the 7 infants aged 12½ to 24 hours, a left-to-right shunt was observed in 5. In one of these, a 14 hour-old infant, the left-to-right shunt was 35% of pulmonary flow. In the other 4 cases, the shunt was either not demonstrable in the LA→pAo curves or too small to be quantitated by the present technic. Accordingly systemic blood flow could not be estimated. Nevertheless, for comparative purposes only the systemic blood flow in these 4 cases and in 5 others were assumed to roughly equal pulmonary flow and were plotted in the scattergram in figure 2 and figure [illegible]. These were, however not included in the derivation of the mean values in Table 1 since, strictly speaking, systemic blood flow should have been less than the corresponding

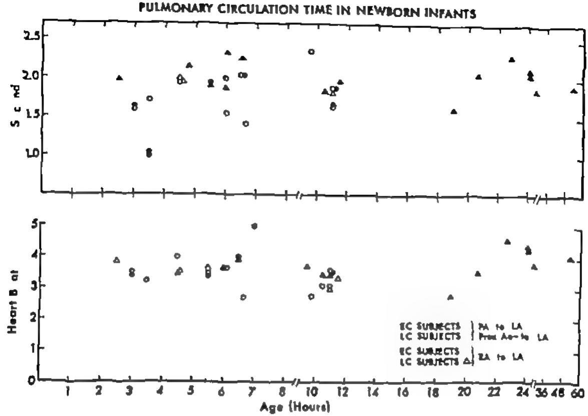

Fig 5 Pulmonary circulation time (in seconds and in heart beats) in the newborn period

pulmonary blood flow since PBF=RVO +L → R shunt) right ventricular output (also equivalent to systemic blood flow in the absence of a L → R shunt at atrial level) systemic vascular resistance, left-to-right shunt, and right-to-left shunt observed in the EC and LC subjects in various age groups The results did not differ significantly in the two groups of subjects.

A left to-right shunt was observed in 34 of 37 infants studied during the first 24 hours. In the majority of these, the shunt represented *less than 50 % of the left ven*tricular output, corresponding to pulmonary systemic flow ratios of less than 0 1 0 (fig 6) The ductal (arteriosus) origin of the shunt was verified by the pAo → LA dye curves except in 6 cases where the confirmatory curves were for technical reasons, not obtained In some cases where the LA → pAo dye curves did not reveal any shunt configuration, the pAo → LA curves demonstrated a small ductal shunt (fig 7) The forward triangle area of the pAo → LA curve was not compared to that of the LA → pAo curve to estimate the relative size of the shunt flow because of the likelihood of incomplete mixing in the proximal aortic chamber and of streaming of the injected dye to the ductal orifice Thus, in *some instances* where pAo → LA curves were repeated at 3- to 6-minute intervals, the curves sometimes varied *significantly* Physiologic changes, e.g transient ductal constriction, could have been contributory factors.

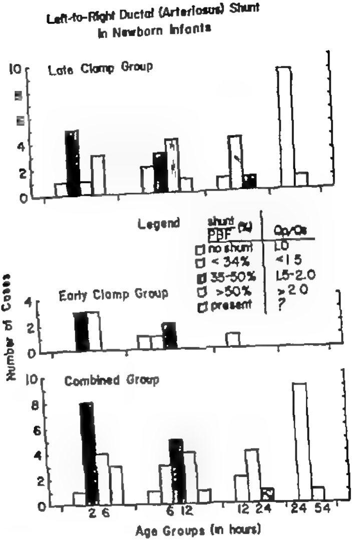

Fig. 6. Relative frequency of left-to-right shunts in the newborn period.

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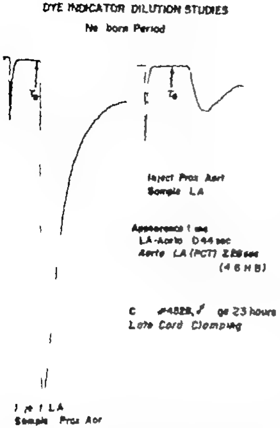


Fig 7 Dye dilution curves of a 23-hour-old LC infant showing no demonstrable shunt pattern in the LA $\rightarrow$ pAo curve but a definite left-to-right ductal shunt in the pAo $\rightarrow$ LA curve

pulmonary flow In 10 infants 25 to 54 hours of age, no shunt pattern was observed in the LA $\rightarrow$ pAo curves. However in a 41 hour-old infant, the pAo $\rightarrow$ LA curves demonstrated a tiny ductal shunt. In 2 other cases, age 25 hours and 29 hours no pAo $\rightarrow$ LA dye curves were obtained to confirm the absence of a ductal left to-right shunt.

A right to-left shunt was noted in only 7 of 45 cases studied and all 7 cases were less than 12 hours of age (fig 9) Verification of the shunt was obtained through repeat injections in the inferior vena cava (or ductus venosus) site which demonstrated a consistent right to-left shunt curve pattern. The size of the shunt was small and varied between 4 % to 7 % of systemic blood flow In 1 case, the shunt was observed only during sampling from the descending aorta and not from the proximal aorta, thus localizing the shunt at the ductus arteriosus level In 3 cases where sampling at the proximal aortic site was not made, shunting across the atrial septum may or may not have been present in addition to that at the ductal level Similarly in 2 cases where the shunt pattern was observed at both aortic sampling sites, shunting could have been at either the atrial level only or at both the atrial and ductal sites.

Pulmonary vascular resistance was calculated in 2 EC and 6 LC subjects and was expressed in resistance units (1 P.R.U = 80 dynes sec. cm^{-5}) This was related to the corresponding systemic resistance in the form of a pulmonary systemic vascular resistance ratio (fig 9) which was felt to be more appropriate for comparative purposes.

Systemic vascular resistance was estimated in 10 EC and in 24 LC infants. The resistance values ranged between 11 5 to 51 3 P.R.U (fig 9) Those of the LC infants were not significantly higher than those of the EC infants. A notable finding was the decline in systemic vascular resistance by the later part of the first day At age 2 to 12 hours, mean systemic resistance of the LC subjects was 30 3 P.R.U $\pm$ 34 S.E. at age 25 to 54 hours, corresponding values were 19 6 P.R.U $\pm$ 32 S.E. ($P<0\ 001$) This change coincided with the reduction or disappearance of the left-to-right shunt and with the increase in systemic blood flow Thus at age 2 to 12 hours, the mean systemic blood flow was 1 96 L/min/M^2 $\pm$ 0 154 S.E., whereas at age 25 to 54 hours it was 3 54 L/min/M^2 $\pm$ 0 238 S.E. ($P<0\ 001$)

Functional patency of the ductus venosus was demonstrated in all of 20 subjects test

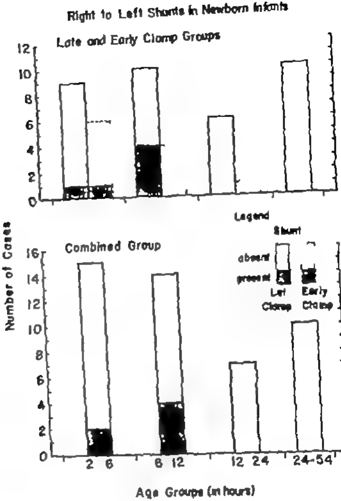
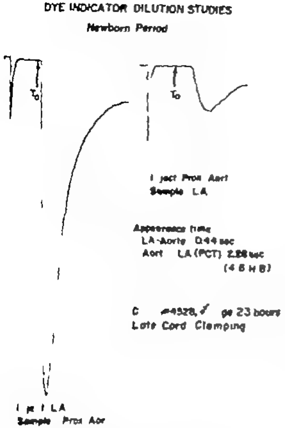


Fig 8 Relative frequency of right-to-left shunts in the newborn period

ed, ranging in age from 3 to 26 hours This was indicated by an umbilical venous injection curve of nearly similar appearance time and configuration to that following *right atrial injection, but with smaller area* since some of the injected dye must have passed directly into the liver by way of the portal circulation. The appearance time of the umbilical venous injection curves was, in general, only slightly longer than that of the right atrial injection curves, the average difference being 0 60 second ± 0.50 S D This slight delay was ascribed to the traversal of the dye across the umbilical vein and constricted ductus venosus. As a rule, the area of the umbilical venous injection *dye curves, relative to that of the right atrial* injection curves, was larger in the very young infants than in the older ones (fig 3) However reproducibility of the curves using varying umbilical venous injection sites was not tested. For this reason, a comparison of the forward triangle area of the umbilical injection curve with that of the



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Functional patency of the ductus venosus was demonstrated in all of 20 subjects test

(5 12) These studies were performed chiefly on adults, utilizing peripheral venous or right heart injection and ear lobe or peripheral arterial sampling The proportionality factor (K) of 0 37 and 0 34, established for the forward triangle method in these investigations, represents the ratio of the forward triangle portion to the entire primary curve area, obtained after venous or right heart injection. From 55 left atrial-to-proximal aortic dye curves of 6 LC newborn infants without shunts, we obtained a mean K value of 0.254±0 005 S.E. (11) This factor was accordingly adopted in the present study (see Appendix II)

Implicit in the forward triangle method of cardiac output estimation is the assumption that a constant relationship exists between the forward triangle area of the dye curve and that of the entire primary curve. However, this proportionality may vary slightly in different curves, and this limits the accuracy of this method. In our analysis of the 55 normal LA → pAo curves, the mean difference between the output values obtained by the forward triangle method and the Stewart Hamilton method was 0 051 L/min with a standard deviation of 0 074 (S E ±0.010) Expressed in terms of percent of the Hamilton output value, the mean difference was — 7 6%±11 S.D It is obvious then that isolated instances of gross inaccuracy can occur Nevertheless, for reasons already given, it seems to be the only feasible method of cardiac output estimation presently available in these tiny subjects with left-to-right shunts. This limitation can be minimized by performing repeat dye curves at 2 to 3-minute intervals and deriving the mean output value from 3 or more technically satisfactory curves.

The reproducibility of the dye curves in the present study was comparabl to that found in older subjects by densitometry (6, 7 10 22) or by the Fick method (19 24) It is worth emphasizing that cardiac output values obtained by the present or by any other method are, at best, only an approximation of the actual. This also holds true for other related determinations, namely shunt flow pulmonary vascular resistance, and systemic vascular resistance.

Shunt quantitation by the method used in this study and by others (13) may theoretically speaking, be somewhat over estimated since shunt peak concentration truly represents a summated deflection resulting from the shunt flow and the primary curve exponential decay slope upon which the former is superimposed. The use of an identical K factor of 0.254 for the estimation of the shunt curve area may also be questioned (11) However, Krovetz and Gessner (13) have shown good correlation between the calculated shunts determined by this technic and those determined by oximetry

Our findings of a left-to-right shunt in these term newborn infants during the first day conform with the observations of others based on oximetry data (13 20) However in some instances the shunt may persist longer, as in our 45-hour-old infant with a tiny ductal shunt. Obviously the above observations apply only to normal, full-term infants and not to premature infants, which represent a totally different subject material

Right-to-left shunts have been observed with high frequency during the first hour of life but not by the second hour using the same dye dilution technic presently d scribed (9) From our data, it appears that this shunt, which is small and physiologically insignificant, may still occur at age 2 to 12 hours in about 20% of normal in-

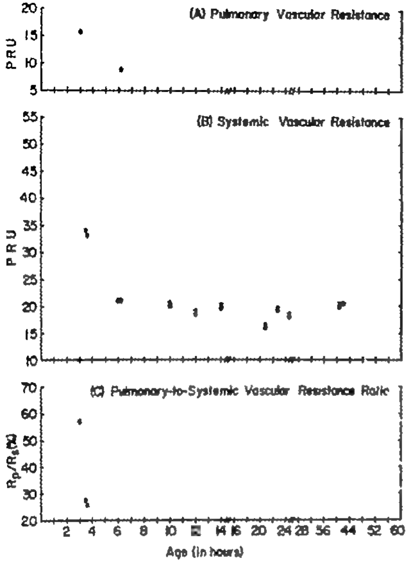

Fig 9 Pulmonary vascular resistance (A) and systemic vascular resistance (B) plotted against age In (C) the two ha e been related in the form of pulmonary systemic resistance ratio The circles with crosses in scattergram (B) refer to the same cases in figure 2 where systemic flow was assumed to equal pulmonary flow

corresponding right atrial injection curve was not made. Theoretically this may have roughly indicated the size of the liver by pass through this route relative to that of the total venous return to the right atrium.

DISCUSSION

Recent studies (9 13) including the present one, demonstrate that the dye dilution technic is applicable for cardiac output and shunt estimation in newborn infants. The method is, however not simply a miniaturized version of that used in older children or adults In the presence of a left to-right shunt, peripheral venous or even right atrial injection is not valid for output estimation since the rapid pulmonary circulation time results in appearance of the shunt flow at about the time of peak concentration with consequent distortion of the primary curve. Separation of the primary curve from the rest of the tracing by logarithmic extrapolation of the disappearance slope is not possible in this situation.

The forward triangle method of cardiac output estimation has been shown to be comparable to the Stewart Hamilton method

of age. A tiny right-to-left shunt was observed only in 7 of 30 infants up to 12 hours of age. Systemic blood flow which was low during the first day increased by the second or third day accompanied by a decline in systemic vascular resistance. The pulmonary and systemic vascular resistance indices were higher than those of normal older children.

No significant differences in the hemodynamic findings of the two groups of infants were observed. Functional patency of the ductus venosus was observed in all 20 subjects tested.

APPENDIX I

Appearance time corrected for catheter delay time (CDT)

(a) $AT = AT - CDT$

where

AT = corrected appearance time
AT = uncorrected appearance time

(b) $CDT = \frac{V}{R} \times 0.6$

where

V = volume of catheter-to-cuvette dead space (ml)
R = pump withdrawal rate (ml/sec)
0.6 = K factor (23)

APPENDIX II

Cardiac output estimation by the forward triangle method

$$CO = \frac{60 \times I}{\frac{1}{2} \times BT \times PC} \times K$$

where

CO = cardiac output (ml/min)
I = dye injected (mg)
BT = build-up time (sec)
PC = peak concentration (mg/L)
K = 0.254 = factor relating forward triangle portion ($\frac{1}{2}\ BT \times PC$) of primary curve to its total area.

fants (fig. 8) Its comparatively higher incidence in the LC subjects than in the EC subjects although not statistically significant, is perhaps related to the high pulmonary artery pressures in the LC infants which tend to remain close to systemic range during the first 7 to 9 hours after birth (3)

A noteworthy finding in this study was the low systemic blood flow during the first day (fig 2 and Table 1) Its increase thereafter coincided with and is presumably related to the disappearance of shunting across the ductus arteriosus. If a cause-and effect relationship truly existed in this circumstance, the possibility of inadequate left ventricular output in the face of the volume overload from the ductal L → R shunt may have to be incriminated

Systemic vascular resistance during the first day is greater than that reported for normal older children (2, 16) this is related to the low systemic flow By the second day systemic arterial pressure and flow are augmented, but the increase in systemic flow is relatively greater indicating a decline in systemic vascular resistance (fig 9) The calculated pulmonary vascular resistances of 8 newborn infants were likewise all above the normal range of 1 to 3 P.R.U observed in normal older children (14, 16) To what extent vasoconstriction contributes to this high resistance state of the newborn pulmonary vascular bed cannot be commented upon in this study Also, it is not possible to state whether pulmonary vascular resistance in the LC subjects differs from that in the EC subjects due to the insufficient number of cases studied (fig 9)

The present data provide some baseline values for comparison with those obtained from abnormal subjects in the same age group The findings also suggest that the circulatory system of the normal term, neonate adapts effectively to varying degrees of placental transfusion and blood volume. When this adaptation is successfully accomplished is not known, but, from our studies at least, it must occur shortly after birth. The high atrial pressures in the LC newborn infants drop to normal levels during the first hour (4) However pulmonary arterial pressures in these subjects remain significantly higher than those in EC infants for several hours (3)

The absence of significant hemodynamic differences between the two groups of subjects in this study does not negate the possibility that these differences may have been demonstrable at age 1 or 2 hours.

The significance of transient patency of the ductus venosus after birth is not known. It is conceivable that the magnitude of the flow through this structure (which represents a liver by pass) could significantly influence liver function in the human newborn.

SUMMARY

Dye dilution studies by the double catheter technic were performed on 47 normal, term, newborn infants 2½ to 54 hours of age. According to the time of cord clamping, the subjects were divided into two groups (1) early clamp group — 11 infants and, (2) late clamp group — 36 infants

Cardiac output and left to-right shunt were calculated from the LA → pAo curves and, in eight instances, from the PA → LA curves by the forward triangle method. A left-to-right shunt across the ductus arteriosus was generally observed during the first day although at age 1 to 24 hours this shunt was already very small It was noted in only 1 of 10 infants over 24 hours

of age. A tiny right-to-left shunt was observed only in 7 of 30 infants up to 12 hours of age. Systemic blood flow which was low during the first day increased by the second or third day accompanied by a decline in systemic vascular resistance. The pulmonary and systemic vascular resistance indices were higher than those of normal older children.

No significant differences in the hemodynamic findings of the two groups of infants were observed. Functional patency of the ductus venosus was observed in all 20 subjects tested.

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Appearance time corrected for catheter delay time (CDT)

(a) $AT = AT - CDT$

where

AT = corrected appearance time
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(b) $CDT = \frac{V}{R} \times 0.6$

where

V = volume of catheter-to-cuvette dead space (ml)
R = pump withdrawal rate (ml/sec)
0.6 = K factor (25)

APPENDIX II

Cardiac output estimation by the forward triangle method

$$C.O. = \frac{60 \times I}{\frac{1}{2} \times BT \times PC} \times K$$

where

$C.O.$ = cardiac output (ml/min)
I = dye injected (mg)
BT = build-up time (sec)
PC = peak concentration (mg/L)
$K = 0.254$ = factor relating forward triangle portion ($\frac{1}{2}\ BT \times PC$) of primary curve to its total area.

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Appearance time corrected for catheter delay time (CDT)

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where

AT = corrected appearance time
AT = uncorrected appearance time

(b) $CDT = \frac{V}{R} \times 0.6$

where

V = volume of catheter-to-cuvette dead space (ml)
R = pump withdrawal rate (ml/sec)
0.6 = K factor (25)

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Cardiac output estimation by the forward triangle method

$$C.O. = \frac{60 \times I}{\frac{1}{2} \times BT \times PC} \times k$$

where

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I = dye injected (mg)
BT = build-up time (sec)
PC = peak concentration (mg/L)
k = 0.254 = factor relating forward triangle portion ($\frac{1}{2}$ $BT \times PC$) of primary curve to its total area.

fants (fig 8) Its comparatively higher incidence in the LC subjects than in the EC subjects, although not statistically significant, is perhaps related to the high pulmonary artery pressures in the LC infants which tend to remain close to systemic range during the first 7 to 9 hours after birth (3)

A noteworthy finding in this study was the low systemic blood flow during the first day (fig 2 and Table 1) Its increase thereafter coincided with and is presumably related to the disappearance of shunting across the ductus arteriosus. If a cause-and effect relationship truly existed in this circumstance, the possibility of inadequate left ventricular output in the face of the volume overload from the ductal L → R shunt may have to be incriminated.

Systemic vascular resistance during the first day is greater than that reported for normal older children (2 16) this is related to the low systemic flow By the second day systemic arterial pressure and flow are augmented, but the increase in systemic flow is relatively greater indicating a decline in systemic vascular resistance (fig 9) The calculated pulmonary vascular resistances of 8 newborn infants were likewise all above the normal range of 1 to 3 P.R.U observed in normal older children (14 16) To what extent vasoconstriction contributes to this high resistance state of the newborn pulmonary vascular bed cannot be commented upon in this study Also it is not possible to state whether pulmonary vascular resistance in the LC subjects differs from that in the EC subjects due to the insufficient number of cases studied (fig 9)

The present data provide some baseline values for comparison with those obtained from abnormal subjects in the same age group The findings also suggest that the circulatory system of the normal, term, neonate adapts effectively to varying degrees of placental transfusion and blood volume. When this adaptation is successfully accomplished is not known, but, from our studies at least, it must occur shortly after birth. The high atrial pressures in the LC newborn infants drop to normal levels during the first hour (4) However pulmonary arterial pressures in these subjects remain significantly higher than those in EC infants for several hours (3)

The absence of significant hemodynamic differences between the two groups of subjects in this study does not negate the possibility that these differences may have been demonstrable at age 1 or 2 hours.

The significance of transient patency of the ductus venosus after birth is not known. It is conceivable that the magnitude of the flow through this structure (which represents a liver by pass) could significantly influence liver function in the human newborn.

SUMMARY

Dye dilution studies by the double catheter technic were performed on 47 normal, term, newborn infants ½ to 54 hours of age. According to the time of cord clamping, the subjects were divided into two groups (1) early clamp group — 11 infants and, (2) late clamp group — 36 infants

Cardiac output and left-to-right shunt were calculated from the LA → pAo curves and in eight instances, from the PA → LA curves by the forward triangle method A left-to-right shunt across the ductus arteriosus was generally observed during the first day although at age 12 to 24 hours this shunt was already very small It was noted in only 1 of 10 infants over 24 hours

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APPENDIX III

Estimation of left-to-right shunt (13) (see also fig 1)

$$\text{shunt (\% of PBF)} = \frac{\Delta B}{\Delta A + \Delta B} \times 100$$

where

PBF = pulmonary blood flow (left ventricular output)
ΔB = forward triangle area of shunt curve ($\frac{1}{2}$ BT $\times PC_s$)
ΔA = forward triangle area of primary curve ($\frac{1}{2}$ BT $\times$ PC)

Note

$$BT = (tp_s - t_a) - PCT$$

where

BT = build-up time of shunt curve
tp_s = peak concentration time of shunt curve
t_a = appearance time of primary curve
PCT = pulmonary circulation time

APPENDIX IV

Estimation of right to-left shunt (see also fig 1)

$$\text{shunt (\% of SBF)} = \frac{\Delta C}{\Delta C + \Delta D}$$

where

SBF = systemic blood flow (right ventricular output)
ΔC = forward triangle area of shunt curve ($\frac{1}{2}$ BT $\times PC_s$)
ΔD = forward triangle area of primary curve ($\frac{1}{2}$ BT $\times$ PC)

Note

$$BT = (t_p - t_a) - PCT$$

where

BT = build-up time of primary curve
t_p = peak concentration time of primary curve
t_a = appearance time of shunt curve
PCT = pulmonary circulation time

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QUANTITATIVE STUDIES OF THE HUMAN NEONATAL CIRCULATION

III. OBSERVATIONS ON THE NEWBORN INFANT'S CENTRAL CIRCULATORY RESPONSES TO MODERATE HYPOVOLEMIA

by

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Among the various potential hazards during the adaptation of the newborn infant to extrauterine life, systemic circulatory hypotension may be mentioned as a possible cause for defective institution of pulmonary function. The background for this reasoning, with respect to the central circulatory pattern is that systemic hypotension may jeopardize the pulmonary perfusion by reducing the aorto-pulmonary pressure gradient and thereby diminishing or possibly reversing the left right shunt through the patent ductus arteriosus. As this shunt may be assumed to promote adequate pulmonary perfusion, particularly during the establishment of pulmonary function in the immediate neonatal period, its reduction or absence might result in impairment of the ventilation/perfusion ratio of the lung and delayed closing of the foramen ovale. It has also been implied that impaired pulmonary perfusion may adversely affect the mechanical characteristics of the expanding neonatal lung and thereby the work of breathing (19).

In the search for possible pathogenetic links between the perinatal circulatory adaptation and respiratory dysfunction in the newborn infant, the capacity of the newborn to maintain systemic blood pressure homeostasis has accordingly been investigated. Experimental procedures have included studies of blood pressure control during body tilting (14, 2) and during acutely induced hypovolemia (19, 3). It has been concluded from the latter studies that changes of the blood volume in the range 10—25 per cent of predicted total blood volume (PTBV) are capable of inducing considerable blood pressure drop on the arterial as well as on the venous side of the circulation. These findings were interpreted as indicating that the newborn's capacity to adapt its vascular volume to the available blood volume is less well developed than later in life.

Earlier studies of blood pressure homeostasis during blood volume alterations lacked information regarding the effect on cardiac output, central shunting and resistance. However, simultaneous evaluation of the roentgenological heart size and appearance of the pulmonary vessels in chest films indicated a pronounced effect on the stroke and minute volume of the heart as well as the vascular volume of the lungs.

The present investigation was undertaken in order to study with more sophisticated quantitative methods the effect of moderate hypovolemia on the newborn infant's central circulatory pattern with special regard to cardiac output, pulmonary circulation and central shunts.

MATERIAL AND METHODS

Six normal fullterm infants, ranging in age from 7 to 28 hours and in weight from 3.3 to 3.8 kg constitute the subject material for the present study. All of the babies were products of normal gestations and their perinatal and postnatal course was judged uneventful. They were all vertex deliveries and the umbilical cord was ligated when pulsations had ceased, usually not earlier than two minutes after delivery of the trunk. The babies were usually investigated,

(18) Immediately after withdrawal of the blood a new set of recordings was made and a further blood volume depletion of the same magnitude was performed. During this second stage of hypovolemia, corresponding to a total depletion of 15 per cent of PTBV new recordings of flow and pressures were made. The blood was thereafter re-infused and a set of final tracings recorded. Each stage lasted approximately five minutes, and no attempts were made to study the circulatory effect of prolonged hypovolemia.

In order to avoid changes of catheter position between tracings both catheters were tightly secured to the umbilical stump during the whole procedure. The body temperature of the babies usually did not change significantly and was maintained whenever necessary by heat radiation. Room temperature was in the range 25—27°C. Statistical analysis of data was performed according to standard methods on an IBM 1130 Data Processor.

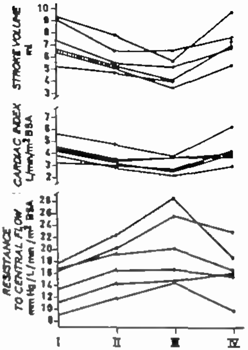


Fig. 1. Stroke volume, blood flow and resistance to blood flow as calculated in the ascending portion of the aorta. Roman symbols I—IV stand for control observation, depletion with 7.5 per cent of PTBV, depletion with 15 per cent of PTBV and observation after restitution of blood volume respectively.

RESULTS

The circulatory consequences of hypovolemia are listed in Table I and are graphically reproduced in Fig. 1. There is in all instances a statistically significant reduction of the left ventricular output following PTBV depletion of 7.5 per cent. This decrease is further accentuated in five of the cases when the depletion is doubled, but remains almost unchanged in the sixth case.

The average reduction in cardiac output during the initial depletion amounts to 191 ml/min, which corresponds to 20 per cent of the initial recording. The average additional reduction during the second stage of depletion is 107 ml/min, which makes a total of 298 ml/min or 33 per cent of the baseline value. The restitution of blood increased the cardiac output in 2 cases slightly above initial levels, in 2 to a level slightly below the initial observation and in the remaining 2 cases the cardiac output returned to a level considerably lower than the initial observation.

The heart rate was only slightly affected during the hypovolemic state and the drop in left ventricular output was therefore almost entirely due to reduction of the stroke volume. Stroke volume dropped 24 per cent during the first stage of hypovolemia and to a total of 40 per cent during the second stage. Aortic mean pressure was

with exception of the youngest ones in whom feeding had not been initiated 1—2 hours after a meal and were therefore usually sleeping during the entire procedure Hemoglobin as well as hematocrit readings were within normal limits for the age.

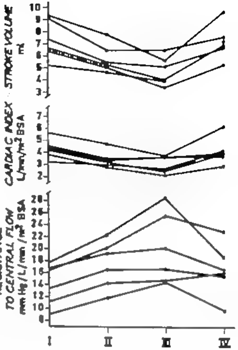
The procedure and technique used to assess the cardiac output has recently been described in detail (9) and shall only be briefly outlined. After appropriate sterile preparation of the umbilical stump an infant feeding tube size F 5 was advanced through the umbilical vein and the ductus venosus to the right and subsequently to the left atrium. The left atrial location of the catheter was checked by monitoring the pressure curve and, if considered neccessary by determination of the oxygen saturation of the blood An identical feeding tube was subsequently advanced through one of the umbilical arteries and placed above the ductus arteriosus in the ascending aorta. The location of this catheter was confirmed in two instances by pull back from the left ventricle and in the remaining four cases by the identification of a left right ductal shunt following dye injection into the aorta and sampling from the left atrium Both catheters were connected to pressure transducers and pressure recordings from the aorta and atria were made The pressure signals were recorded together with an ECG signal on a direct writing multichannel instrument To keep the catheters free of clots they were occasionally flushed with 1—2 ml physiological saline containing 0 2 per cent heparin.

Dye dilution studies In order to assess the left ventricular output 0 2 mg Cardiogreen® was injected into the left atrium (LA) and blood was sampled from the ascending aorta (Ao) by continuous withdrawal at a rate of 15 ml/min through a densitometer cuvette The dilution curve was recorded on a writer with linear output, a chart width of 25 cm and a response time of 0 9 second for 90 % of the total deflection. The attenuator of the recorder was set to give a 15—20 cm deflection for the peak concentration of the primary curve Due to sterile preparation of the cuvette the blood could be returned to the infant after every tracing Calibration of the instrument was made according to a technique earlier described (9) using the infants own blood. Quantitative evaluation of the dilution curve was made by use of the forward triangle method (10) revised in this laboratory for application to the newborn infant (9) Left ventricular minute output was computed as the mean of at least three technically acceptable dye dilution curves Dye injections were made within the shortest possible interval, usually not exceeding two minutes. The heart rate was obtained by continuous ECG recording during the injection and sampling. Systemic blood pressure was recorded immediately before and after each tracing Resistance to blood flow in the ascending aorta was estimated from the left ventricular minute output and the aortic mean pressure and expressed in central resistance units (CRU) as mm Hg/1/min/m^2 BSA. The relative magnitude of the left right shunt through the ductus arteriosus could usually be assessed from the recirculation deflection on the descending part of the LA Ao primary dye curve (12)

After initial basal determination of the parameters under investigation hypovolemia was induced step-wise in the following manner An amount corresponding to 7 5 per cent of the predicted blood volume was withdrawn into a heparinized syringe The blood volume of the infant was predicted from the age and weight of the infant under study according to available literature data

(18) Immediately after withdrawal of the blood a new set of recordings was made and a further blood volume depletion of the same magnitude was performed. During this second stage of hypovolemia, corresponding to a total depletion of 15 per cent of PTBV new recordings of flow and pressures were made. The blood was thereafter re-infused and a set of final tracings recorded. Each stage lasted approximately five minutes, and no attempts were made to study the circulatory effect of prolonged hypovolemia.

In order to avoid changes of catheter position between tracings both catheters were tightly secured [redacted] the umbilical stump during the whole procedure. The body temperature of the babies usually did not change significantly and was maintained whenever necessary by heat radiation. Room temperature was in the range 25—27°C. Statistical analysis of data was performed according [redacted] standard methods on an IBM 1130 Data Processor



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of hypovolemia the central resistance increased some 40 per cent and during the second stage an average increase of 58 per cent above the initial observation was recorded.

A functional patency of the ductus arteriosus was demonstrated in all cases and was also verified by interchanging injection and sampling sites. Right atrial injection prior to hypovolemia demonstrated a small right left shunt through the foramen ovale in only one of the cases. Pulmonary circulation time, measured as the difference in appearance time between right and left atrial injections and sampling in the ascending aorta, varied between 1.6 and 2.3 seconds. Changes in the pulmonary transit time during hypovolemia could not be studied as right-sided injections were not performed during depletion. The left-right shunt through the ductus arteriosus was small or insignificant in 3 instances on the initial observation, whereas in the remaining 3 cases there was a 40—55 % per cent shunt present. During hypovolemia no consistent change in the size of these shunts could be traced, and the ratio peak primary dye curve deflection to peak shunt deflection remained unchanged throughout. It is noteworthy that in one infant with insignificant ductal shunt on initial as well as hypovolemic dye curves, a 45 per cent left-right ductal shunt was present after restitution of blood volume.

DISCUSSION

Data from the literature pertaining to the cardiovascular response to hypovolemia are somewhat conflicting. Warren et al. (21) stat that bleeding normal man 5—15 per cent of his total blood volume does not significantly change systemic mean pressure, peripheral resistance or cardiac output. Contrary to this statement others have reported pronounced reduction of stroke volume and minute volume but well maintained systemic pressures during moderate hypovolemia (13, 17). Whereas it has been suggested that adult man is capable of systemic blood pressure homeostasis in the presence of acute bleeding not exceeding 30 per cent of the estimated total blood volume (1) a marked systemic hypotension has been reported after considerably less pronounced blood volume depletions in the newborn infant (19). It would seem appropriate to relate the hypovolemic response not only to the volume depleted but also to the composition of the subject material investigated, time factors etc.

Ralston et al. (17) performed dye dilution studies in adult man during blood volume depletion of the same relative magnitude as those in the present investigation, and report an average decrease in cardiac output of 15 per cent with a stroke volume reduction of 12 per cent. Systemic pressures remained more or less unchanged with a 10 per cent average increase of the vascular resistance. With a comparable degree of hypovolemia it is evident that, whereas systemic perfusion pressure is equally well maintained, cardiac output and systemic vascular resistance are considerably more affected in the newborn infant. There are at least two valid explanations for this difference. One is related to the presence of a ductal shunt in most of the infants studied, and the other to a more pronounced effect on the venous filling of the heart in the newborn infant.

Since our measurements of cardiac output refer to the actual left ventricular output, a change in magnitude of functioning ductal shunt must influence the calculated minute output of the left ventricle. Reduc

Table I Circulatory data during various stages of graded hypovolemia Roman symbols I—IV stand for control observation, depletion with 7 5 per cent of PTBV depletion with 15 per cent of PTBV and observation after restitution of blood volume respectively HR=heart rate. CI=cardiac index SV= stroke volume. CRU=central resistance units (mm Hg/L/min/M²BSA) L R and R L symbolise the presence of shunts through ductus arteriosus and foramen ovale (0=no shunt, (+)=small or insignificant shunt, +=shunt estimated less than 30 per cent of LV output ++=shunt estimated in excess of 30 per cent of LV output)

No	BW gm	Age hr	Volemic stage	S	D	M	HR	CO l/min	CI	SV ml	CRU	L-R	R-L
1	3300	27	I	74	54	62	119	0 754	3 77	6 3	16 4	(+)	0
			II	70	46	55	110	0 545	2 73	5 0	20 1	0	0
			III	60	48	52	124	0 410	2 05	3 3	25 4	0	
			IV	74	50	63	110	0 555	2 78	5 1	22 7	0	
2	3800	7	I	53	37	50	115	1 042	4 53	9 1	11 0	++	0
			II	60	40	50	125	0 795	3 46	6.4	14 2	++	
			III	60	41	51	126	0 805	3 50	6.4	14.6	++	
			IV	75	45	58	113	0 838	3 65	7 4	15 9	++	
3	3450	14		70	50	59	125	0 912	4 34	7 3	13 6	++	0
			II	62	44	54	127	0 689	3.28	5 4	16 5	++	
			III	62	45	51	129	0 647	3 08	5 0	16 6	+	
			IV	77	56	64	135	0 876	4.17	6.5	15 4	++	
4	3560	16	I	63	47	53	129	0 675	3 21	5 2	16 5	0	(+)
			II	66	44	55	131	0 605	2 88	4.6	19 1	(+)	
			III	58	40	49	135	0 515	2 45	3 8	20 0	0	
			IV	80	55	65	119	0 834	3 97	7 0	16 4	++	
5	3680	14	I	62	43	50	125	1 167	5 56	9 3	9 0	++	0
			II	60	44	56	128	0 995	4.74	7 7	11 8	+	
			III	64	48	53	139	0 765	3 64	5 5	14 5	++	
			IV	66	49	59	134	1 270	6 05	9 5	9 8	++	
6	3430	30	I	80	62	74	134	0 885	4 21	6 6	17 6	0	0
			II	82	58	70	131	0 662	3 15	5 1	22 2	0	
			III	74	58	68	133	0 504	2 40	3 8	28.3	0	
			IV	84	58	71	121	0 805	3 83	6 6	18 5	(+)	

only moderately affected both during the first and second stage, and as a rule there was an overshoot of the aortic pressures after blood volume restitution. Left atrial mean pressure decreased considerably during the smaller depletion when an average pressure drop of 2 5 mm Hg mean pressure was recorded. There was as a rule no further decrease in this pressure during subsequent depletion A slight overshoot was also noted in the left atrial pressure during the final recording

The resistance to blood flow in the ascending aorta which, in the presence of an open ductus arteriosus reflects the combined resistance of the systemic and pulmonary circulation increased considerably during hypovolemia. *During the first stage*

of hypovolemia the central resistance increased some 40 per cent and during the second stage an average increase of 58 per cent above the initial observation was recorded.

A functional patency of the ductus arteriosus was demonstrated in all cases and was also verified by interchanging injection and sampling sites. Right atrial injection prior to hypovolemia demonstrated a small right-left shunt through the foramen ovale in only one of the cases. Pulmonary circulation time, measured as the difference in appearance time between right and left atrial injections and sampling in the ascending aorta, varied between 1.6 and 2.3 seconds. Changes in the pulmonary transit time during hypovolemia could not be studied as right-sided injections were not performed during depletion. The left-right shunt through the ductus arteriosus was small or insignificant in 3 instances on the initial observation, whereas in the remaining 3 cases there was a 40—55 per cent shunt present. During hypovolemia no consistent change in the size of these shunts could be traced, and the ratio peak primary dye curve deflection to peak shunt deflection remained unchanged throughout. It is noteworthy that in one infant with insignificant ductal shunt on initial as well as hypovolemic dye curves, a 45 per cent left-right ductal shunt was present after restitution of blood volume.

DISCUSSION

Data from the literature pertaining to the cardiovascular response to hypovolemia are somewhat conflicting. Warren et al. (21) state that bleeding normal man 5—15 per cent of his total blood volume does not significantly change systemic mean pressure, peripheral resistance or cardiac output. Contrary to this statement others have reported pronounced reduction of stroke volume and minute volume but well maintained systemic pressures during moderate hypovolemia (13, 17). Whereas it has been suggested that adult man is capable of systemic blood pressure homeostasis in the presence of acute bleeding not exceeding 30 per cent of the estimated total blood volume (1), a marked systemic hypotension has been reported after considerably less pronounced blood volume depletions in the newborn infant (19). It would seem appropriate to relate the hypovolemic response not only to the volume depleted but also to the composition of the subject material investigated, time factors etc.

Ralston et al. (17) performed dye dilution studies in adult man during blood volume depletion of the same relative magnitude as those in the present investigation, and report an average decrease in cardiac output of 13 per cent with a stroke volume reduction of 12 per cent. Systemic pressures remained more or less unchanged with a 10 per cent average increase of the vascular resistance. With a comparable degree of hypovolemia it is evident that, whereas systemic perfusion pressure is equally well maintained, cardiac output and systemic vascular resistance are considerably more affected in the newborn infant. There are at least two valid explanations for this difference. One is related to the presence of a ductal shunt in most of the infants studied, and the other to a more pronounced effect on the venous filling of the heart in the newborn infant.

Since our measurements of cardiac output refer to the actual left ventricular output, a change in magnitude of functioning ductal shunt must influence the calculated minute output of the left ventricle. Reduc

tion of the ductal shunt may be occasioned by a diminished pressure gradient between aorta and the pulmonary artery or by a con striction of the ductal lumen. Dye dilution patterns during the hypovolemic stages however did not indicate any significant change in the relative magnitude of the duc tal shunt If it is assumed that the intrinsic pumping capacity of the myocardium remains unchanged during hypovolemia, the reduced left ventricular output must be related to a decreased filling of the right heart, and this effect is evidently more pronounced in neonates than in normal adult man.

Maintainance of venous return during hemorrhage is achieved chiefly by constric tion of the post-capillary or capacitance vessels resulting in a centripetal redistribu tion of blood with mobilization of pooled venous blood The constrictive capacity of the capacitance vessels or the actual tone of these vascular compartments will consequently be the controlling factor in the maintainance of venous return to the right heart. In animal experiments it has been shown that the mean circulatory pressure (the pressure in the circulatory system in the absence of flow) which is affected by the tonus of the capacitance vessels, is also related to venous return to the heart and drops considerably during hemorrhage (7 8)

The possibility that the effect on the mean circulatory pressure is more pronounc ed in the newborn infant is in agreement with the earlier reported finding (19) that the newborn s capacity to adapt its vascular volume to actual total blood volume is less well developed than later in life The impressive response of the systemic vascular resistance recorded in the present investiga tion should be regarded as indicating that the infant is struggling by means of its impressive vaso-motor control (3 20) to establish blood pressure homeostasis in the presence of a markedly reduced cardiac out put.

Although in the present investigation we have not studied changes occuring in the pulmonary circulation, our data allow some conclusions to be drawn In the absence of a right left shunt at the atrial level the pulmonary blood flow must be considered identical with the left ventricular output in these infants As no significant shunt was recorded at this level prior to the hypovolemic situation, the reduction of the left ventricular output must have been paralelled or even exceeded by that in the pulmonary circulation. If it is accepted, with due respect to our limitations in assessing these para meters, that ductal resistance as well as the relative magnitude of ductal blood flow did not significantly change during hypovolemia, the aorto-pulmonary pressure gra dient must have been well maintained. This would imply that the resistance of the pul monary vascular bed has increased concomitantly with the reduction of the pul monary blood flow

Our knowledge regarding the control of pulmonary vascular resistance in the new born is mostly derived from studies in ani mals and pertains particularly to the late fetal and immediate neonatal period We know from these investigations that the pul monary resistance in the perinatal period is subject to variations in response to a number of stimuli Whereas vaso-dilatation is caused by increasing the oxygen tension in the alveoli or decreasing the carbon dioxide tension (11) merely by the ventilation of the collapsed lung (4) or by the administra tion of acetylcholine (14) vasoconstriction is reported to occur during the opposite

condition (25 11) It is evident that at least with respect to the response to catecholamines the late fetal pulmonary vessels of the lamb react much the same as does the systemic circulation (2) Although to our knowledge no study has been reported with respect to the excretion and effect of catecholamines during hypovolemia at this age, it is tempting to assume that the increase in vascular tone of the systemic and pulmonary circulation is mediated through the action of adrenergic substances.

Whereas the effect of the pulmonary circulation of hypervolemia is well studied, reports on the effect of hypovolemia are scarce. DeFreitas et al. (6) demonstrated that during pooling of blood in the four extremities of normal man cardiac output decreased an average of 16 per cent with concomitant rises in pulmonary vascular resistance of 11 per cent and in systemic resistance of 18 per cent From these studies it would appear that in adult man hypovolemia causes a more pronounced hypotension in the pulmonary circulation. It is probably not feasible from the present studies to say whether the capacity of the pulmonary circulation to increase vascular resistance is equally or better developed in the newborn infant.

In an earlier investigation of the circulatory response to hypovolemia in the newborn infant we concluded that whereas bleeding approximately 10 per cent of the total blood volume does not seem to affect systemic blood pressure markedly depletion of amounts corresponding to 20—25 per cent of the blood volume resulted in a fall in both systemic and pulmonary blood pressures From indirect observations it was suggested that hypovolemia in the newborn was characterized by a diminished stroke and minute volume Although the earlier investigation is not quite comparable with respect to subject material, the results in the present investigation seem to be in good agreement with the earlier observations. They suggest that the normal infant is usually capable of maintaining systemic blood pressure if blood loss does not exceed 10—15 per cent of PTBV It is very likely that the greater blood volume depletion of the earlier study exceeded the capacity of vasomotor control. From experiments in adult man this is known to occur when bleeding exceeds some 30 per cent of the total blood volume (1) It would seem that this limit is lower in the newborn infant, due mainly to the more pronounced effect on venous return to the heart.

The question of possible adverse effects of hypovolemia on respiratory function during the perinatal period may relate to the effects of lowered pulmonary perfusion as well as decreased pulmonary blood volume and pulmonary arterial pressure on the mechanical behaviour of the lungs. From the present investigation it may be concluded that moderate hypovolemia does not interfere with the central shunt pattern, and that systemic circulation is not being maintained at the expense of pulmonary perfusion. The fact remains, however that pulmonary blood flow is markedly reduced during hypovolemia, and may impair the ventilatory function of the lungs. It has recently been pointed out (16) that a newborn infant deprived of the placental transfusion demonstrates typical signs of hypovolemia, and has a significantly higher clearance of carbon dioxide and a higher oxygen saturation than do infants who have received this transfusion. It is tempting to interpret this as a result of a change in ventilation/perfusion relationships of the lungs. The finding that early-clamped infants exhibit a sig

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A reduction of central blood volume may conceivably alter the mechanical characteristics of the lungs. Although recent studies of acute bleeding in normal man suggest that pulmonary blood volume is kept fairly constant (6 24) intrathoracic blood volume, including the large vessels and the heart which are known to reduce their volume during hypovolemia (19) may produce changes in respiratory mechanics It has, indeed been shown (15) that low initial blood volume in the newborn infant is associated with high V_{FRC} and pulmonary compliance, an effect that would be expected to reduce the work of breathing.

It may probably be stated that after respiration is established moderate hypovolemia does not have any adverse effect on this respiration. Whether there may be adverse effects during the initiation of breathing must be studied in the delivery room. Investigations along these lines are in progress as a logical continuation of the present investigation

SUMMARY

6 newborn infants 7—28 hours old were investigated with respect to changes in cardiac output, central circulatory pattern and vascular resistance after blood volume depletions of 7 5 per cent and 15 per cent of predicted total blood volume. Concomitant with a marked drop in left ventricular output and stroke volume, resistance to flow in the ascending aorta increased considerably but systemic blood pressure was only moderately affected Hypovolemia caused no demonstrable change in the size of the ductal shunt which was demonstrated in 5 of the cases. The recorded drop in stroke and minute volume is considerably greater than that occurring after corresponding blood volume depletion in the adult. The background for this difference is discussed. It is suggested that hypovolemia exerts a more pronounced effect on the venous return to the heart due to less efficient control of the capacitance vessels in the newborn.

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QUANTITATIVE STUDIES OF THE HUMAN NEONATAL CIRCULATION

IV OBSERVATIONS ON THE NEWBORN INFANT'S PERIPHERAL CIRCULATION AND PLASMA EXPANSION DURING MODERATE HYPOVOLEMIA

by

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In a foregoing communication (29) it was pointed out, that whereas the left ventricular output decreased considerably during a moderate reduction of the total blood volume in the newborn infant, systemic blood pressure was well maintained as a consequence of increased vascular resistance. The efficiency with which this was achieved indicates a very capable vasomotor control in the newborn in response to hypovolemia. It also prompts a further appreciation of its role in the regulation of systemic blood pressure.

Whereas the technical set-up and procedures for the evaluation of the central circulatory pattern usually are complicated and require access to intravascular compartments, methods for the study of peripheral blood flow are less cumbersome. The most commonly used technique for the study of peripheral circulation is that of venous occlusion plethysmography where the arterial inflow to a limb or parts of it is measured as volume increase of the segment after occlusion of the venous outflow. This technique has been widely used and values compare well with those obtained by more direct flow metering devices (13). Since the plethysmographic method measures volume changes in a section of the limb defined by the plethysmograph, the flow figures are given in terms of blood flow per unit time per unit tissue volume (ml/min/100 ml).

Occlusion plethysmography has been adapted for use in newborn infants, and the peripheral circulation has been analysed both in health and disease and during various experimental conditions. It has been demonstrated that blood flow in the extremities is greater and resistance to flow less in the newborn than in adult man (6). It has also been pointed out that this difference is considerably more pronounced in the premature infant (6, 22). Recent studies indicate that the newborn asphyxiated infant, as well as the normal infant exposed to hypoxic environment, increases peripheral resistance considerably (6) and it has also been shown that resting blood flow may increase drastically during reactive hyperemia of the limb (5).

That portion of peripheral blood flow which supplies the skin has attracted special attention due to its heat regulating properties. Whereas an absolute quantitation of this flow requires special methods, changes occurring in the cutaneous circulation may be traced by monitoring the skin temperature (11, 7). The vascular control of cutaneous circulation in the newborn infant has been thoroughly investigated (1) and it is today well documented that the newborn responds to temperature stimuli with great variations in skin blood flow.

It is evident from the cited reports that the vascular tone of the peripheral circulation is already actively participating in circulatory and metabolic control during the first hours of life. The present investigation was undertaken to study the circulatory changes induced in the calf of the newborn infant by moderate blood volume reduction. It is the purpose of the study to evaluate the peripheral circulation's function in controlling blood pressure in the neonate.

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MATTRIAL AND METHODS

12 normal fullterm infants constitute the subject material for the study. They were all products of normal gestations and uneventful deliveries. Their birthweights varied between 3190 and 3920 g.m. With respect to age the material may be divided in 3 groups. 4 infants were 1—2 hour old, 4 were 19—23 hours old, and the remaining 4 were between 18 and 58 hours old at the time of the study. Infants in the two latter groups were investigated not earlier than 2 hours after a feeding. The babies were covered with two layers of sterile cloths and were apart from the heat radiating from the operating lamp not exposed to any heating devices. Room temperature was kept at 25—26 C, and the infants were all asleep during the investigation.

Blood pressure measurements. Pressures in the abdominal aorta were recorded via a polyethylene tube (Sterilon P 5) inserted through one of the umbilical arteries. Pressure pulse tracings were made on a direct writing recorder with a simultaneous ECG signal. Systemic mean pressure was calculated from the electrically filtered aortic pressure curve.

Peripheral blood flow. The circulation in the left calf of the infant was measured by venous occlusion plethysmography with an air filled cuff as plethysmograph (8). The width of the cuff was 5 cm and the circumference 9.5—10.5 cm, and it fitted snugly around the middle portion of the calf. Double-cuff occlusion at sub-diastolic values was used to cut off the venous circulation according to principles discussed in the literature (10, 9). The plethysmographic cuff was inflated to 5 cm H_2O and pressure variations occurring in the cuff were recorded together with aortic pressure and the ECG. The limb under study was raised and kept at a level corresponding to the mid axillary line during the investigation. When a steady baseline was obtained venous occlusion was induced by valves preset at 40 mm Hg. The plethysmograph was calibrated with 0.1 ml of air from a Mantoux syringe. A series of tracings was made in quick sequence, the mean of 3 technically good tracings being considered representative for the studied limb. Flow per unit volume tissue was figured by computing tissue volume covered by the plethysmograph. Resistance to blood flow was calculated from the plethysmographic flow values and the simultaneously recorded aortic mean pressure. No allowance was made for right atrial pressure.

Cutaneous blood flow was monitored by continuous recording of the skin temperature of the contralateral calf.

In order to evaluate the effect of blood volume depletion on plasma dilution hematocrit recordings were made in a group of infants before the blood volume depletion and 10, 20, and 30 minutes after.

Blood volume reduction. After an initial basal recording of the various parameters studied, blood volume depletion was induced stepwise by withdrawing into a heparinized syringe first 7.5 per cent of predicted total blood volume (PTBV) and then another 7.5 per cent. Recordings of blood flow, pressure, skin temperature and hematocrit were made after every stage. When 15 per cent of PTBV had been removed the infant was left asleep for 15 minutes, following which a new set of recordings was made and the blood reinfused. After a final observation immediately following restitution of blood volume the catheter was pulled out. Care was taken to ensure that recordings were not made on

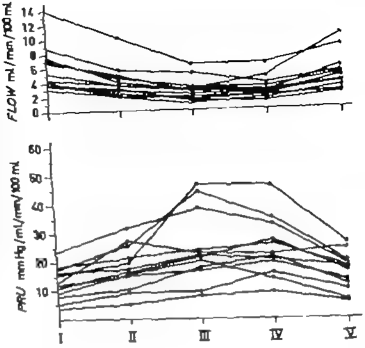

Fig. 1 Peripheral blood flow and vascular resistance as measured in the calf of the newborn infant during graded hypovolemia. PRU = peripheral resistance units. Roman symbols: I = control observation. II = depletion with 7.5 per cent of PTBV. III = depletion with 15 per cent of PTBV. IV = observation 15 minutes after induction of the 15 per cent depletion. V = blood volume restored.

mediately after a spontaneous movement of the leg or foot.

Statistical analyses of data was performed according to standard methods on an IBM 1130 Data Processor.

RESULTS

Pertinent data from the investigation are listed in Table I and values for peripheral blood flow and vascular resistance are also graphically presented in Fig. 1. The aortic mean pressure decreased an average of 2.7 mm Hg after 7.5 per cent depletion and another 5.8 mm Hg when the total amount withdrawn was 15 per cent of PTBV. Prior to the re-infusion of blood arterial mean pressure had risen an average of 2.6 mm Hg as compared to the value recorded immediately after withdrawal. Re-infusion of the blood resulted in an aortic mean pressure overshoot of 3 mm Hg as compared to the control value.

Mean peripheral blood flow was 3.9 ml/min/100 ml for all subjects prior to depletion. The average resistance was 12.5 mm Hg/ml/min/100 ml. Peripheral blood flow decreased and resistance increased in every case after withdrawal of blood.

During the first stage of depletion, peripheral blood flow decreased an average of 34 per cent or 2.0 ml/min/100 ml, and vascular resistance increased 5.2 units or 41 per cent. Both these changes are statistically highly significant ($p<0.01$). Peripheral blood flow decreased another 19 per cent and vascular resistance increased another 53 per cent as compared to the control values ($p<0.01$) after 15 % depletion. The total blood flow reduction in the calf after a 15 per cent reduction of PTBV thus amounted to 53 per cent with a concomitant increase

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Cutaneous blood flow was monitored by continuous recording of the skin temperature of the contralateral calf

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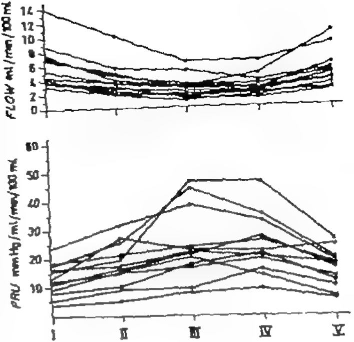

Fig. 1 Peripheral blood flow and vascular resistance as measured in the calf of the newborn infant during graded hypovolemia. PRU = peripheral resistance units. Roman symbol I = control observations. II = depletion with 5 per cent of PTBV. III = depletion with 15 per cent of PTBV. IV = observation 15 minutes after induction of the 15 per cent depletion. V = blood volume restored.

mediately after spontaneous movement of the leg or foot.

Statistical analysis of data was performed according to standard methods on an IBM 1130 Data Processor.

RESULTS

Pertinent data from the investigation are listed in Table I and values for peripheral blood flow and vascular resistance are also graphically presented in Fig. 1. The aortic mean pressure decreased an average of mm Hg after 7.5 per cent depletion and another 3.8 mm Hg when the total amount withdrawn was 15 per cent of PTBV. Prior to the re-infusion of blood arterial mean pressure had risen an average of 2.6 mm Hg as compared to the value recorded immediately after withdrawal. Re-infusion of the blood resulted in an aortic mean pressure overshoot of 3 mm Hg as compared to the control value.

Mean peripheral blood flow was 5.9 ml/min/100 ml for all subjects prior to depletion. The average resistance was 12.5 mm Hg/ml/min/100 ml. Peripheral blood flow decreased and resistance increased in every case after withdrawal of blood.

During the first stage of depletion, peripheral blood flow decreased an average of 34 per cent or 2.0 ml/min/100 ml, and vascular resistance increased 5.2 units or 41 per cent. Both these changes are statistically highly significant ($p<0.01$). Peripheral blood flow decreased another 19 per cent and vascular resistance increased another 53 per cent as compared to the control values ($p<0.01$) after 15% depletion. The total blood flow reduction in the calf after a 15 per cent reduction of PTBV thus amounted to 53 per cent with a concomitant increase

MATERIAL AND METHODS

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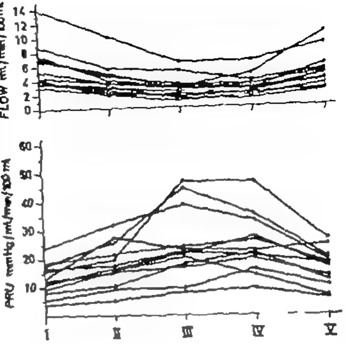

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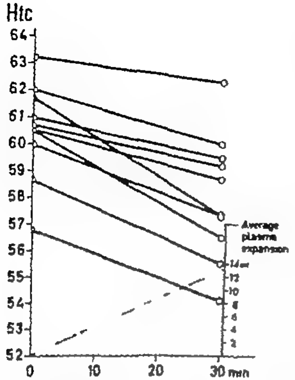

Fig 2 Change in hematocrit reading during the hypovolemic situation Shaded area represents estimated plasma volume expansion

in vascular resistance of 94 per cent. Reappraisal of the situation after 15 minutes showed an inconstant pattern and the average values for flow and resistance did not change

Whereas in two cases the peripheral blood flow was significantly higher after restitution and vascular resistance less than before depletion, the majority of cases had lower peripheral flow and higher resistance at the end of the investigation

Temperature response Rectal temperature was usually very well maintained with an average increase during hypovolemia of +0.2°C. Changes in cutaneous temperature were small and inconsistent with an average increase during hypovolemia of 0 03 C. Actual temperature changes in the individual cases are listed in Table 1

Hematocrit response Numerical values for the venous hematocrit are listed in Table 1 and the change in hematocrit is graphically reproduced in Fig 2 for the approximately 25-minute period between the first withdrawal and the restitution of blood volume. The average fall in hematocrit during this time period amounted to 2.31 per cent. There was no indication that the drop in hematocrit was related to the initial hematocrit reading

The magnitude of the parameters studied did not seem to be correlated to the age of the patient nor to the weight group.

DISCUSSION

Various types of venous occlusion plethysmography have been used in earlier investigations of the peripheral blood flow of the newborn infant. Riley (22) who was the first to apply the technique quantitatively to the newborn, used an air filled plethysmograph and reported a mean blood flow in the hand and forearm of the full term newborn infant of 5.2 ml/min/100 ml. Celander (3) working with a water filled plethysmograph covering the foot and calf of the infant arrived at mean values of 7 9 ml/min/100 ml in the healthy newborn. In a recent study (14) an average value of 9 6 ml/min/100 ml is given for the calf blood flow with a straingauge plethysmographic principle where volume changes are recorded as variations of the impedance of a conducting system encircling the limb studied The present figures of 5 9 ml/min/100 ml tissue for the calf of the fullterm infant as well as those of Riley using the same technique are thus somewhat lower than those reported with different plethysmographic techniques Existing differences may probably be explained by dissimilarities

TABLE I

Table I Data on the peripheral circulatory pattern in twelve infants during graded hemorrhage Roman symbols I—V represent control observation, depletion with 7.5 per cent of PTBV depletion with 15 per cent of PTBV prolonged observation after 15 per cent depletion and observation after restitution of blood volume, respectively HR = heart rate PF = peripheral blood flow SD = standard deviation. PRU = peripheral resistance units. HTC = hematocrit. ST = skin temperature RT = rectal temperature x, xx, xxx interposed between two figures relates to the degree of statistically significant difference (x = 0.05 > p > 0.01 xx = 0.01 > p > 0.001 xxx = p < 0.001) Symbols below figures in Stage V relate to comparison with control observation.

No.	BW	Age	Volume stage	S	D	M	HR	PF	SD ±	PRU	HTC	ST	RT
1	3920	2	I	78	50	60	131	6.8	1.23	9.0	61.0	28.1	35.2
								xxx		xxx			
			II	70	46	56	156	3.9	0.53	15.0		28.[illegible]	
			III	70	46	58	147	2.9	0.26	20.3		28.0	
								x		xxx			
			IV	72	50	60	147	4.4	0.97	14.0	59.5	28.4	
			V	80	52	62	145	10.1	0.61	6.4		29.2	36.7
								xxx		xxx			
2	3350	2	I	72	44	54	110	4.2	0.32	12.1	60.5	33.6	35.5
								xxx		xxx			
			II	60	40	50	112	1.9	0.45	27.0		33.2	
			III	52	34	44	120	1.9	0.52	24.2		33.0	
			IV	52	36	42	125	1.8	0.25	22.2	58.7	33.0	
			V	72	44	54	108	2.5	0.12	24.3		33.0	35.7
								x		xxx			
3	3920	1.5	I	68	48	58	124	3.8	0.20	15.4	60.7	33.0	35.1
										xxx			
			II	68	46	58	146	3.0	0.21	19.5		33.2	
								xxx		xxx			
			III	60	42	52	150	1.3	0.35	47.2		33.2	
			IV	62	40	55	155	1.2	0.35	46.5	59.2	33.2	
			V	70	42	56	124	2.2	0.20	26.2		31.0	36.2
								xxx		xxx			
4	3520	2	I	70	44	56	130	3.2	0.29	17.6	56.8	33.2	36.2
								xxx		xxx			
			II	62	40	52	129	2.0	0.15	25.5		33.2	
								x		xxx			
			III	54	36	48	138	1.1	0.26	44.6		33.1	
			IV	—	—	46	138	1.3	0.06	35.0	53.8	33.0	
			V	68	44	[illegible]	127	3.0	0.29	19.6		33.0	35.2

No	BW	Age	Volemic stage	S	D	M	HR	PF	SD ±	PRU	HTC	ST	RT
5	3190	26	I	66	40	52	130	14.0	1.11	3.7	62.0	33.6	36.5
			II	58	35	50	120	10.1 xxx	1.81	5.0 xx		33.6	
			III	54	36	48	135	6.4	1.25	7.7		33.7	
			IV	60	40	56	125	6.3	0.69	8.9	60.0	34.0	
			V	76	48	56	144	8.5 xxx	0.15	6.6 xxx		35.9	36.5
6	3000	19	I	68	42	54	110	7.0 xxx	0.46	7.8 xxx	58.7	33.8	36.3
			II	56	36	48	126	4.8 xxx	0.06	10.0 xxx		34.0	
			III	56	40	46	124	2.6	0.31	17.9 xxx		34.0	
			IV	56	44	50	115	2.4	0.30	21.4	56.0	34.0	
			V	80	50	66	100	3.7	0.71	11.7 xxx		34.0	36.7
7	3010	26	I	70	50	56	133	3.2	0.15	17.7 xxx	—	—	36.6
			II	68	42	56	122	2.7	0.06	21.0			
			III	60	40	48	144	2.3	0.25	20.6 xxx			
			IV	66	42	58	123	2.2	0.25	26.2			
			V	88	60	78	124	4.3 x	0.40	17.3			36.7
8	3270	24	I	66	34	47	120	8.8 xxx	1.08	5.4 xxx	—	33.-	36.7
			II	63	36	49	129	5.6	0.50	8.8		33.4	
			III	51	30	40	140	5.1 x	0.53	8.6 xxx		33.4	
			IV	62	37	5	127	3.5	0.49	15.2		33.4	
			V	84	62	50	128	5.0 xxx	0.55	10.0 xxx		33.6	36.6
9	3600	48	I	78	48	58	116	5.3 xxx	0.06	10.7 xxx	60.0	—	36.6
			II	70	47	56	117	3.5	0.20	16.0 xxx			
			III	60	40	52	146	2.7	0.38	19.3 xxx			
			IV	76	50	62	130	2.3	0.17	26.9	57.3		
			V	84	52	62	135	3.6 xxx	0.00	17.2 xxx			36.4

N	BW	AW	Volemic stages	S	D	M	HR	PF	SD ±	PRU	HTC	ST	RT
10.	3200	38	I	92	70	82	140	3 5 xxx	0 17	23 6 xxx	60 5	33.0	36.3
			II	82	54	72	122	3	0 15	31 7 xxx		33	
			III		46	58	130	1 5	0 25	38.(xxx		33 4	
			IV	70	50	60	122	1.8	0..3	32.8	56.5	33 5	
			V	110	68	8	120	4.5	0.25	19 3 xxx		33.4	36.5
11	3330	52	I	81	58	72	123	7 1 xxx	0.61	10.2 xxx	63 3	34.3	36 1
			II	72	54	68	140	4 5 xx	0 21	15.0 xxx		34.2	
			III	66	44	51	132	3 2	0 31	16.8 xxx		34 1	
			IV	72	54	62	160	3 1	0 38	20.0	61 8	34 1	
			V	75	50	62	126	4. xxx	0 15	13 1 xxx		34 1	36..
12	3410	[illegible]	I	80	52	66	100	4.3	0 26	15 4 xxx	61 7	34 1	36.7
			II	8	60	68	151	3 6	0 20	17 4 xxx		34 0	
			III	[illegible]	54	66	145	3 0	0 47	22.3		34 0	
			IV	—	—	52	158	2.5	0 40	21 2	5 3	34.0	
			V	80	58	64	143	3 6	0 20	17 9		34 4	36 6

in the methodology and to some extent by different experimental conditions. As existing differences between various methods have no bearing on the interpretation of the present results since each patient serves as his own control, they may be neglected.

The hemodynamic response of the infant to moderate hypovolemia with well maintained systemic blood pressure closely reflects the findings in an earlier investigation on the central circulatory pattern during blood volume depletions of identical magnitude (29). The increase of peripheral resistance that was observed in the earlier investigation has been verified in this study and quantitated with respect to vascular response of the lower limb. The observed *increase in* peripheral resistance seems to be directly proportional to the *degree of hypovolemia*. It is evident that during the 15 per cent depletion, resistance to blood *flow* in the calf of the infant *is almost doubled*. The finding that the average increase in peripheral resistance is considerably larger in the calf than the calculated increase in resistance to flow in the ascending aorta during identical volume depletion suggest the presence of *vascular* compartments where

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			V	76	48	56	144	8.5 xxx	0.15	6.6 xxx		33.9	36.5
6	3000	19	I	68	42	54	110	7.0 xxx	0.46	7.8 xxx	58.7	33.8	36.3
			II	56	36	48	126	4.8 xxx	0.06	10.0 xxx		34.0	
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			V	80	50	66	100	5.7	0.71	11.7 xxx		34.0	36.7
7	3010	26	I	70	50	56	133	3.2	0.15	17.7 xxx	—	—	36.6
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			II	63	36	49	129	5.6	0.50	8.8		33.4	
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infants followed with hematocrit determinations, calculation of the amount of fluid transudated or the percentage of blood volume restoration may be made. For the present material this volume of transudated fluid amounts to 13 ml during the 25-minute interval or an approximate 25 per cent restoration of depleted volume by the time blood is being reinfused. Since the hypovolemia in the present investigation was induced stepwise and the hematocrit determined only once initially and again just prior to the reinfusion of blood, the rate and other characteristics of this fluid transfer cannot be more specifically analysed from the present data. In order to augment these observations a series of 5 infants with comparable birthweight and age were investigated exclusively with respect to changes in hematocrit during prolonged hypovolemia. Readings were made from 5—6 samples taken before and 10, 20 and 30 minutes after the withdrawal of 15 per cent of PTBV. The results are graphically plotted in Fig. 3. It is evident that the fastest plasma expansion takes place immediately after blood withdrawal and that after 10 minutes some 20 per cent of the depleted volume has been restored. The total plasma dilution during the 30-minute observation period amounts to some 30 per cent of the withdrawn volume.

Plasma volume expansion after graded hemorrhage has been extensively studied since Starling first stated (26) that posthemorrhagic dilution of blood took place in an effort to restore the circulating blood volume. It has been concluded from animal experiments (21) that the capacity of plasma volume dilution is great enough to restore within a few hours the plasma volume depleted during hemorrhage up to 50 per cent of the TBV. It has also been demonstrated (20) that the posthemorrhagic plasma volume is significantly greater after 24 hours than control values, thus reflecting an attempt to restore the total blood volume. Whereas in the early phases of plasma restoration the mechanism is purely a dilution, in later phases protein concentration rises and attains control values 2 hours post hemorrhage (20).

The presence of a fairly rapid restoration of blood volume in the absence of marked systemic hypotension indicates that it is not systemic pressure per se which is controlling the watershift in the newborn infant. This is in good agreement with results in animals (25, 30) which attest that capillary and not systemic pressure is involved in this mechanism. Experimental investigations in ani-

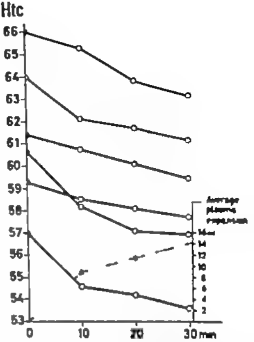

Fig. 3. Change in hematocrit reading after one-step withdrawal of 15 per cent of PTBV. Shaded area represents estimated plasma volume expansion.

vascular response to bleeding is less pronounced or does not exist.

Whereas it is accepted that most of the vascular compartments of the body are in some way engaged in the maintenance of blood pressure homeostasis, the vascular response in some is absent or indefinite. It is well documented that the cerebral blood flow is autoregulated securing perfusion to the brain in the presence of systemic hypotension (2 15) It has also been suggested that the vascular resistance of the skin should not be directly engaged in overall systemic blood pressure control during hemorrhage (12) As the perfusion of these two vascular regions alone in adult man amounts to some 20—30 per cent of the cardiac output, it is easily understood that in the newborn infant, where both spaces are relatively larger these low resistance compartments must be reflected in the central flow resistance

Studies of the regional blood flow in the newborn infant have demonstrated that both cutaneous perfusion (1) limb perfusion (5 6) and possibly also renal blood flow (18) are subject to considerable vasomotor control and seem to react to proper stimuli much the same as the circulation in adult man Our findings imply that the general pattern of response to hypovolemia, with a redistribution of blood in a centripetal direction is the same in the newborn infant as in grown-ups It would seem from the skin temperature recordings that during thermal stability cutaneous circulation does not play a great role in raising the peripheral resistance to conserve systemic blood pressure. Recent findings (19) that skin temperature is reduced as a consequence of blood volume deprivation at the time of birth may imply that the considerably smaller blood volume found in early clamped infants may also be a strong enough stimulus to engage the vasomotor control of the skin in blood pressure homeostasis. A more accurate explanation may however be that the lower skin temperature in these infants is due to thermoregulation, an activity which requires and responds drastically with cutaneous vasomotor regulation

The establishment of a centralized blood perfusion has earlier been demonstrated during neonatal stress (6 23) and also experimentally verified during oxygen deprivation (24) Whereas peripheral vasoconstriction in skeletal muscles evidently is capable of maintaining systemic blood pressure by the centralisation of the blood volume, this is performed at the expense of local muscular blood supply with potential metabolic consequences It is, however well known that perfusion of the resting muscle in man is far greater than the metabolic need with an a v oxygen difference usually not in excess of 30 per cent saturation. Knowing that peripheral perfusion in the newborn infant is almost twice that of the adult (6) it is reasonable to assume that the blood supply to the limb muscles of the newborn must be considerably more reduced than is the case in the present study to be inadequate for the metabolic need of the tissue

Although the circulatory pattern did not seem to be significantly affected by the 15 minutes of prolonged hypovolemia, hematocrit readings indicate that the blood volume deficit is being partly compensated for by restitution of the plasma volume The finding of a mean 3 per cent hematocrit decrease during the 25 minute period between the first withdrawal and the restitution of blood volume reflects fluid transudation from the extravascular compartment Estimating an average PTBV for the 10

infants followed with hematocrit determinations, calculation of the amount of fluid transudated or the percentage of blood volume restoration may be made. For the present material this volume of transudated fluid amounts to 13 ml during the 25-minute interval or an approximate 25 per cent restoration of depleted volume by the time blood is being reinfused. Since the hypovolemia in the present investigation was induced stepwise and the hematocrit determined only once initially and again just prior to the reinfusion of blood, the rate and other characteristics of this fluid transfer cannot be more specifically analysed from the present data. In order to augment these observations a series of 5 infants with comparable birthweight and age were investigated exclusively with respect to changes in hematocrit during prolonged hypovolemia. Readings were made from 5—6 samples taken before and 10, 20 and 30 minutes after the withdrawal of 15 per cent of PTBV. The results are graphically plotted in Fig. 3. It is evident that the fastest plasma expansion takes place immediately after blood withdrawal and that after 10 minutes some 20 per cent of the depleted volume has been restored. The total plasma dilution during the 30-minute observation period amounts to some 50 per cent of the withdrawn volume.

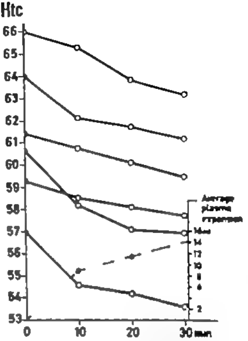

Fig. 3. Change in hematocrit reading after one-step withdrawal of 15 per cent of PTBV. Shaded area represents estimated plasma volume expansion.

Plasma volume expansion after graded hemorrhage has been extensively studied since Starling first stated (26) that posthemorrhagic dilution of blood took place in an effort to restore the circulating blood volume. It has been concluded from animal experiments (21) that the capacity of plasma volume dilution is great enough to restore within a few hours the plasma volume depleted during hemorrhage up to 50 per cent of the TBV. It has also been demonstrated (20) that the posthemorrhagic plasma volume is significantly greater after 24 hours than control values, thus reflecting an attempt to restore the total blood volume. Whereas in the early phases of plasma restoration the mechanism is purely a dilution, in later phases protein concentration rises and attains control values 2 hours post hemorrhage (20).

The presence of a fairly rapid restoration of blood volume in the absence of marked systemic hypotension indicates that it is not systemic pressure per se which is controlling the watershift in the newborn infant. This is in good agreement with results in animals (25, 30) which attest that capillary and not systemic pressure is involved in this mechanism. Experimental investigations in ani

mals have also revealed that during post hemorrhagic plasma expansion transudated liquid is coming from selective areas, one of which is the interstitial compartment of the skeletal muscles (30)

Although it would be difficult and probably meaningless to compare the rate at which plasma is expanded in the experimental animal with that of the newborn, it is of interest to note that the capacity of the newborn human infant to restore plasma volume seems to match that of other species

In view of the fact that the present investigation has shown that there is a very rapid restoration of plasma volume after induced hypovolemia in the newborn the findings in infants with early clamped umbilical cord where considerably more blood may be withheld seems somewhat confusing It has been repeatedly shown (4 16 27) that, whereas infants with late umbilical cord clamping steadily increase their hematocrits as a sign of hemoconcentration, earlyclamped infants who are deprived of presumably 50—100 ml of blood maintain stable hematocrits during the first 6 hours of life and probably also later The fact that the newborn infant in this situation is not fighting desperately to increase its circulating blood volume must be due either to the possibility that the lower blood volume represents normovolemia for the newborn or that there are in the early-clamped infant considerable vascular compartments closed to circulation The finding of a more pronounced metabolic acidosis in these infants may indirectly support this latter assumption. It has been suggested in an earlier communication (28) that the aeration and establishment of perfusion in the neonatal lung may potentially create a condition of hypovolemia in the newborn infant deprived of the placental transfusion. From the present results it is evident that the newborn infant is capable of restoring plasma volume during conditions of artificially induced hypovolemia. The fact that he does not seem to do this when deprived of the placental transfusion implies that the early-clamped newborn is in volumetric balance

SUMMARY

Twelve newborn infants, 1½ to 58 hours old have been investigated with respect to the consequences of graded hemorrhage on peripheral circulation and plasma volume. It has been demonstrated that the newborn infant responds to a hypovolemia corresponding to 15 per cent of predicted total blood volume with a twofold increase of resistance to blood flow in the calf Peripheral vasomotor tone is adequately controlling the systemic blood pressure by decreasing perfusion of the vascular compartments in the calf muscle whereas no indications of a change in the cutaneous blood flow occurred A rapid decrease of the arterial hematocrit reflects efforts to restore the plasma volume

ACKNOWLEDGEMENT

The authors are greatly indebted to Mrs. Ulla Föhrer R.N and Mrs Ingrid Werner for able assistance

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In view of the fact that the present investigation has shown that there is a very rapid restoration of plasma volume after induced hypovolemia in the newborn, the findings in infants with early clamped umbilical cord where considerably more blood may be withheld seems somewhat confusing It has been repeatedly shown (4 16, 27) that, whereas infants with late umbilical cord clamping steadily increase their hematocrits as a sign of hemoconcentration, earlyclamped infants who are deprived of presumably 50—100 ml of blood, maintain stable hematocrits during the first 6 hours of life and probably also later The fact that the newborn infant in this situation is not fighting desperately to increase its circulating blood volume must be due either to the possibility that the lower blood volume represents normovolemia for the newborn or that there are in the early-clamped infant considerable vascular compartments closed to circulation. The finding of a more pronounced metabolic acidosis in these infants may indirectly support this latter assumption It has been suggested in an earlier communication (28) that the aeration and establishment of perfusion in the neonatal lung may potentially create a condition of hypovolemia in the newborn infant deprived of the placental transfusion From the present results it is evident that the newborn infant is capable of restoring plasma volume during conditions of artificially induced hypovolemia. The fact that he does not seem to do this when deprived of the placental transfusion implies that the early-clamped newborn is in volumetric balance.

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QUANTITATIVE STUDIES
OF THE HUMAN NEONATAL CIRCULATION

V. HEMODYNAMIC FINDINGS IN PREMATURE INFANTS WITH AND WITHOUT RESPIRATORY DISTRESS

by

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Among the characteristic features of the premature infant some of the most important pertain to the circulatory system. It has been shown by indirect means (7 10, 13) as well as by direct intravascular observations (14, 15 22) that the premature newborn has significantly lower systemic blood pressure than the infant born at term. It has also been demonstrated that the peripheral circulation of the premature infant is characterized by lower vascular resistance and higher blood flow per unit tissue than in the fullterm newborn (3, 11 21).

Although some difficulties exist in relating the magnitude of the peripheral blood flow studied in one section of a limb to the overall cardiac output, it might be expected that the left ventricular minute volume per unit BSA or body weight should be greater or at least equal to that recorded in fullterm infants. The existence of left-right shunts in the postnatal period may added to a higher systemic demand for perfusion, be expected to tax the left ventricular capacity more than in the newborn infant at term.

The frequent occurrence of atelectases in the immature infant must be regarded as not only a respiratory complication but also potential circulatory hazard. Apart from the hypoxic effect caused by perfusion of non-ventilated areas of lung, the overall increase in pulmonary vascular resistance secondary to atelectasis (19) may result in extra-pulmonary bypass with reduced pulmonary blood flow and increased venous admixture to the systemic circulation.

It has been considered of great importance to study with the aid of earlier described modifications of the Stewart Hamilton technique (8) the central circulatory pattern of the immature infant with and without pulmonary pathology and relate it to the simultaneously assessed peripheral circulation as well as to earlier reported findings in fullterm infants. It was judged equally important from the pathogenetic and possibly also from therapeutic points of view to elucidate possible differences in the circulatory pattern between these three groups of newborn infants. The present communication reports the preliminary results from an investigation which is currently being carried on in our departments.

MATERIAL AND METHODS

10 premature infants consecutively admitted to the neonatal service of the University Hospital, Helsinki, Finland, constitute the material for the investigation. Five of the infants were normal prematures without signs of cardiopulmonary impairment as judged by the lack of cyanosis in room air respiratory rate below 60/min, and without abnormal respiratory retractions. Plain chest x-ray films revealed no pulmonary or cardiovascular pathology in any of these 5 infants. Their birth weights ranged from 1590 to 2290 gm, and their gestational age from 30 to 35 weeks. Apart from close incubator surveillance and in some instances tube feeding, these infants did not receive any specific treatment. Their stay in the hospital was judged uneventful and was terminated as soon as feeding difficulties disappeared.

Table 1 Circulatory data in premature infants without (—) and with, (nr 6—) respiratory distress GA = gestational age. Apg = minute Apgar score LVO = lef ventricular output CI = cardiac index CRU = central resistance units (mmHg/L/min/M²BSA) L-R and R L = lef right ductal shunt and ght left foramen ovale shunt respectively PBF = pulmonary blood flow VA = venous admixture PF and PRU = peripheral blood flow and peripheral resistance units (mmHg/ml/min/ 00 ml) measured in the calf of the infant.

N	BW	Age	GA	Apg	O_2	Ascending Aorta pO_2	pCO	pH	S	[illegible]	M	LVO	CI	CRU	L R % of LVO	R L % of LVO	PBF	VA % of PBF	[illegible]	PRU
1	1990	5	33	7	21	83	37	7 13	49	56	41	1115 ±63	8 51	18		8	1 26	11	3 4	7 5
2	1960	6	30	8	21	60	38	7 37	63	41	51	387	1 19	12.9	0	11	505	12 5	3 61	11 3
3	2130	5	33	7	21	64	43	7.32	53	32	41	383 ±11	3 84	10 7	+	3	566	7	1 6	9 1
4.	2270	6	33	9	21	90	32	7 36	52	30	11	880 ±203	5 13	12 3	59	3	857	25	5 7	8 0
5	2290	3	33	9	1	96	34	7 56	68	45	56	914 ±83	3 72	10.2	60	12	831	15	13 6	1 2
mean	2048	8	34	8		79	33	7 37			47	822	3 33	10 2		8	737	16.5	6.5	8 8
6.	1290	4	34	5	100	126	63	7 6	49	23	36	621 ±60	4 33	8 5	59	3	605	8 0	6 2	6 0
7	1550	16	32	5	100	42	54	7 7	51	31	42	554 ±99	4 13	9 5	0	33	371	3 0	9 1	4 6
8	1530	[illegible]	32	5	100	140	79	7 37	53	33	40	703 ±67	3 6	7 1	37	1	671	11 0	—	—
9	1850	17	31	7	100 IBPP	56	79	7 43	43	35	39	303 ± 2	2 15	18.1	36	13	259	38 0	0 86	46 7
10.	1880	7	32	7	100	56	[illegible]	7 29	52	34	4	896 ±202	6 22	[illegible]	11	13	762	33 0	3 6	11.6
mean	1612	27	3	5		81	51	7 35			10	616	4 33	10 0		11	331	18 5	3 0	17.2
P						<0 3 >0.2		<0 3 >0.2			<0 1 >0 05	<0 2 >0 1	<0 3 >0 2				<0 05 >0 02	<0 1 >0 05	<0 6 >0 5	<0 1 >0.3

The remaining 5 patients all exhibited various degrees of respiratory distress at the time of the study They all had cyanosis while breathing room air respiratory retractions and tachypnea. Radiological examination of the lungs showed the characteristic fine granulated, mottled appearance of hyaline membrane disease. No instances of pneumothorax, emphysematous changes or larger atelectatic areas were identified in the x ray study which was performed just prior to the circulatory investigation. These infants were all breathing 100 per cent oxygen at the time of study Three of the infants in this group had severe pulmonary impairment with aortic blood PO_2 below 60 mmHg while breathing 100 per cent oxygen. The distressed infants were routinely treated with sodium bicarbonate and glucose intravenously (transumbilical route) to combat the metabolic acidosis This treatment was only temporarily interrupted during the study Three of these infants were sick enough to be considered suitable candidates for intermittent positive pressure breathing (IPPB) Whereas the most severely affected baby (n:o 9) who expired at age 4 days from the disease was connected to the respirator (Bennett Mod.PR2) prior to the circulatory study and was kept on assisted ventilation during the investigation, the other 2 were submitted to this treatment the following day The remaining 2, least affected infants ran a less dramatic course with spontaneous recovery and were free of symptoms at the age of 6—10 days. The child who expired exhibited typical pulmonary pathology of hyaline membrane disease. The infants in the respiratory distress group varied in birth weight from 1290 to 1880 gm, and their gestational age from 31 to 34 weks Further data pertaining to the whole material are listed in *Table I*

The techniques used for the study of the central as well as peripheral circulation have been described in some detail in foregoing communications (8) All infants were investigated laying on the extractable tray of an Isolette[1] Incubator The automatic heat control of the incubator was engaged and whenever neccessary additional heat was provided by a radiating lamp It was usually easy to maintain body temperature with the automatic temperature control unit monitored by a rectal probe

For the peripheral studies, the right leg of the infant was raised to approximately sternal level and the plethysmographic cuff with a circumference of 8.5—9 5 cm and width of 2 5 cm was attached to the leg just distal to the knee. The proximal occlusion was applied to the mid portion of the thigh. Plethysmographic pressure was kept at 5 mm Hg and occlusion pressures at 30—40 mm Hg When a good basal state was attained 3 recordings were made in rapid succession, the leg was lowered again, and the cuffs removed The baby was now covered with sterile cloths and one of the umbilical arteries and the umbilical vein catheterized with a F 5 feeding tube. The venous catheter was advanced to the right atrium where blood was withdrawn for gas analyses. The arterial catheter was placed in the ascending aorta where blood samples were collected for analyses. Right atrial position of the venous catheter was checked by pressure recordings and gas analyses and the position of the aortic catheter by pull back from the left ventricle (4 cases) or by the detection of a ductal shunt in the ascending aorta-to-left atrial dye dilution study

In addition to right atrial and ascending aorta samples blood was also taken from the

1 Air Shields Inc Hatboro, Pa, U S A

Table 1 Circulatory data in premature infants without (nr. 1—5) and with (nr. 6—10) respiratory distress. GA = gestational age. Apgar = 1 minute Apgar score. LVO = left ventricular output. CI = cardiac index. CRU = central resistance units (mmHg/L/min/M²BSA). L-R and R-L = left-right ductal shunt and right-left foramen ovale shunt respectively. PBF = pulmonary blood flow. VA = venous admixture. PF and PRU = peripheral blood flow and peripheral resistance units (mmHg/ml/min/100 ml) as measured in the calf of the infant.

N	BW	Age	GA	Apg	O_2	Ascending pO_2	pCO	pH	Aorta S	[redacted]	M	LVO	CI	CRU	L-R % of LVO	R-L % of LVO	PBF	VA % of PBF	PF	PRU
1	1590	5	33	7	21	83	27	7.43	49	36	11	1115 ±65	8.51	18	0	8	1026	11	5.4	7.5
2.	1960	6	30	8	21	60	58	7.37	63	11	51	587	1.19	12.9	0	11	505	12.5	3.61	11.5
3	2150	5	35	7	21	61	43	7.32	55	52	11	583 ±11	5.81	10.7	+	5	566	?	1.6	9.1
4.	2270	6	35	9	21	90	52	7.36	52	30	11	880 ±705	5.13	12.3	59	5	857	25	5.7	[redacted]
5	2790	20	35	9	1	96	31	7.36	68	15	56	911 ±65	5.72	10.2	60	12	831	15	13.6	4.2
mean	2048	8	34	8		79	55	7.57			17	822	5.53	10.2		8	737	16.5	6.5	8.8
6	1290	4	34	5	100	126	63	7 6	49	25	56	621 ±60	4.55	8.3	59	5	605	28.0	6.2	6.0
7	1530	16	32	5	100	42	51	7.27	54	31	1	551 ±99	4.13	9.5	0	33	371	5.0	9.1	1.6
8	1550	[redacted]	32	5	100	140	[redacted]	7.57	55	33	40	703 ±67	5.62	7.1	37	1	674	11.0	—	—
9	1850	17	31	7	100 IBPP	56	29	7.43	43	35	59	505 ±72	2.15	18.1	56	15	239	58.0	0.86	16.7
10.	1880	7	32	7	100	56	78	7.15	5	34	12	896 ±202	6..	[redacted]	11	15	62	35.0	3.6	11.6
mean	1612	27	32	5		84	51	7.55			10	616	4.55	10.0		11	551	?8.5	5.0	17.2
P						<0.3 >0.2		<0.3 >0.2			<0.1 >0.05	<0.2 >0.1	<0.3 >0.2				<0.05 >0.02	<0.1 >0.05	<0.6 >0.5	<0.1 >0.3

left atrium for blood gas analyses. Determinations of pH, PCO_2 and PO_2 were made with an Astrup micro-assembly (Radiometer, Denmark) and hemoglobin was determined by standard procedures. Pressures in the aorta and atria were monitored on an oscilloscope and recorded on a direct writing instrument (Mingograf 34, Elema Schönander). The calculation of resistance to blood flow was made from the electrically filtered mean pressure recorded in the ascending aorta without corrections for right atrial pressures.

The left ventricular output (LVO) was estimated by the dye dilution principle according to methods earlier described (8). Indicator material (Cardiogreen®) was injected into the left atrium, blood being sampled from the ascending aorta. A modified concept (8) of the forward triangle formula (13) was used for the calculation of left ventricular output. Densitometer calibration was performed with the infant's own blood in two 5 ml syringes well mixed with known amounts of dye. Virtually no blood was lost during the investigation since withdrawn blood was reinfused after calibration and subsequent dye curves.

The magnitude of the right-left shunt through the foramen ovale was estimated by injection of dye into both right and left atria and sampling from the ascending aorta (26). The magnitude of the left-right shunt through the ductus arteriosus was calculated according to techniques described in the literature (12). Pulmonary blood flow was considered identical with the left ventricular output minus existing right-left shunt through the foramen ovale.

The intrapulmonary admixture of venous blood,[1] i.e. non-effective pulmonary blood flow, was computed from the values for pulmonary and left ventricular blood flow, the oxygen content of right atrial, ascending aortic and mixed venous blood (5). The latter figure was derived from values for the left-right ductal shunt and the oxygen content of right atrial and ascending aortic blood. The oxygen content of the various blood samples was computed from oxygen saturation figures corresponding to the temperature and pH corrected PO_2 values (17, 23). Although the resulting figures for intrapulmonary venous admixture must be considered only gross approximations, due primarily to instability of the circulatory pattern, it was considered of interest to make a comparison of this factor in the two groups studied.

RESULTS

The results of the present investigation are listed in Table I together with other data pertaining to the 10 premature infants studied. The mean value for LVO and Cardiac Index is approximately 20—25 % smaller in the group with distressed infants. The mean aortic pressure is reduced correspondingly in the respiratory distress (RD) group and the central resistance to blood flow, accordingly, remains unchanged. Whereas the left-right ductal shunt seems to be of the same magnitude and frequency in the two groups, the right-left shunt through foramen ovale is approximately twice as great in the RD group. Added to the difference in LVO this results in a marked difference in pulmonary blood flow (PBF) between the two groups. This difference which averages 223 ml/min is also statistically probably significant ($p<0.05$). Venous admixture to pulmonary venous blood (VA) is almost twice as large in the

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1 see appendix

distressed group, amounting to nearly 30 per cent of the total pulmonary blood flow. The peripheral circulatory pattern did, somewhat surprisingly, not differ very much between the groups. It is only in the most severely affected child that peripheral vascular resistance is very elevated and peripheral blood flow correspondingly reduced to less than 1 ml/min/100 ml tissue.

Although many of the mean values of the various parameters studied differ considerably between the two groups, it is only the difference in calculated pulmonary blood flow that has a degree of statistical significance. It should be mentioned in this regard that the magnitude of the central shunts which partially constitute the basis for calculation of PBF and VA varied considerably in the same patient irrespective of the clinical condition of the infant. The value used for the calculation of the above parameters was that measured temporally nearest to other inter-related observations.

DISCUSSION

The results of the present investigation may be discussed from two standpoints. The first involves a comparison with data obtained in fullterm infants to elucidate possible differences with respect to the quantitative circulatory pattern between term newborn infants and healthy premature infants. The second point of interest concerns the differences in the circulatory pattern recorded in premature infants with and without respiratory distress and the identification of characteristic hemodynamic features of the disease.

Relationships between term newborn infants and premature infants without respiratory distress. In an earlier communication from this laboratory (1) circulatory data including quantitation of cardiac output were reported for a group of late-clamped infants born at term. These infants may from the circulatory point of view be considered representative for the normal fullterm. Circulatory data obtained in a group of these late-clamped infants in the same post partum age range as the present material has consequently been used as control material.

A comparison between the circulatory data in these two groups of infants substantiates the suspicion that the premature newborn has a relatively much higher cardiac output than the infant born at term. Whereas in the late-clamped fullterm infants 2—24 hours old the cardiac index was found to be 3.31 L/min/M²BSA, the corresponding figure for the healthy premature was 5.5. The finding that the resistance to central flow in the premature is only slightly more than ⅓ of the 28.7 mm Hg/L/min/M²BSA reported for the term infants suggests that the actual work of the left ventricle in the premature infant is only moderately increased. This is illustrated by the finding that left ventricular work index (kgm/min/M²BSA) is 3.5 in the premature as compared with 2.8 for the fullterm infants. The lower resistance to central blood flow is parallelled by a lower peripheral vascular resistance, where the value 8.8 mm Hg/ml/min/100 ml compares with 1..3 reported earlier for *fullterm infants* of the same age (27).

The presence of large left-right shunts through the ductus arteriosus in some of the premature infants studied makes it difficult to assess the effect of pulmonary vascular resistance on the computed central resistance (CRU) values. The fact that the CRU value is approximately the same whether or not the left-right ductal shunt is present suggests that the resistance to central blood flow is

left atrium for blood gas analyses. Determinations of pH, PCO_2 and PO_2 were made with an Astrup micro-assembly (Radiometer Denmark) and hemoglobin was determined by standard procedures. Pressures in the aorta and atria were monitored on an oscilloscope and recorded on a direct writing instrument (Mingograf 34 Elema Schonander). The calculation of resistance to blood flow was made from the electrically filtered mean pressure recorded in the ascending aorta without corrections for right atrial pressures.

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The results of the present investigation are listed in Table I together with other data pertaining to the 10 premature infants studied. The mean value for LVO and Cardiac Index is approximately 20—25 % smaller in the group with distressed infants. The mean aortic pressure is reduced correspondingly in the respiratory distress (RD) group and the central resistance to blood flow accordingly remains unchanged. Whereas the left-right ductal shunt seems to be of the same magnitude and frequency in the two groups, the right-left shunt through foramen ovale is approximately twice as great in the RD group. Added to the difference in LVO this results in a marked difference in pulmonary blood flow (PBF) between the two groups. This difference, which averages 223 ml/min, is also statistically probably significant ($p<0.05$). Venous admixture to pulmonary venous blood (VA) is almost twice as large in the

[1] see appendix

resistance. As this infant was the only one who was ventilated with IPPB during the investigation it may be questioned whether the increased intrapulmonary pressure may have been responsible for the reduced cardiac output. This is known to occur in the healthy lung (28). Restudying the pressure curves from the right and left atria, however, we were able to show that the pressure transmitted to the circulatory system was only a fraction of that applied to the airways and interference with the circulatory dynamics might hence be considered small. It is reasonable to suggest that the applied pressures are absorbed by the stiffened lung parenchyma.

The only available data in the literature related to the quantitative aspects of the circulation in premature infants with respiratory distress are those of Chu et al (4) and Stahlman et al (24), both unfortunately without critical evaluation of the methods used for determination of cardiac output and pulmonary blood flow. While the former group is able to show a reduced effective pulmonary blood flow in affected infants, the latter suggests that pulmonary perfusion in toto may be higher than in the normal premature infant. Our results are opposed to the latter statement but seem to agree with the suggestion of Chu et al. Whereas these authors report an effective pulmonary circulation in the range of 100—150 ml/min in RD cases as compared to 300—450 in normal prematures, corresponding figures in our material are calculated to 350 and 640 ml/min respectively.

The matter of intrapulmonary venous admixture in normal and respiratory distress cases has been studied rather intensely in the past years. Berggren (2) postulated that breathing oxygen for a period of 20—30 minutes would entirely abolish all venous admixture due to diffusion disturbances and a remaining desaturation in arterial blood is explained by the presence of real right-left shunts. Whereas it has been possible earlier to demonstrate with this technique the presence of a true right-left shunt in the newborn infant (15, 16, 18, 20, 25), it has not been possible to separate the intrapulmonary fraction of this shunt from the overall venous admixture. The presence of an intrapulmonary venous admixture, which has been possible to identify and quantitate with the present technique during oxygen breathing, suggests the presence of a true intrapulmonary right-left shunt in the distressed infants. As no circulatory quantitations were performed during oxygen breathing in the healthy prematures the two groups are not directly comparable. It may nevertheless be of interest to observe that venous admixture in the distressed group in spite of oxygen breathing was well above the average for the healthy group in four of the five patients. This indicates that the part of the venous admixture which is due to true right-left shunting within the lung is relatively much greater in the affected infants than would be suggested from the difference in the average VA figure.

It would seem that the pathophysiological background for the cyanosis commonly accompanying respiratory distress in the newborn infant is at least twofold. Whereas the intrapulmonary venous admixture during oxygen breathing is with all probability secondary to a diminished ventilation/perfusion ratio, the extrapulmonary right-left shunt is related to the reduced pulmonary blood flow and/or impairment of right ventricular function. The therapeutic implications affirm that these infants should be treated to improve the pulmonary ventilation as well as perfusion.

mainly governed by other vascular compartments. Whereas big left-right ductal shunts were common findings in both groups the presence of right-left shunts through the foramen ovale in all the studied prematures is contrary to the finding in full-term infants (1) where shunts at this level were rare. In spite of the presence of shunts at the atrial level the pulmonary blood flow in the normal premature infants considerably exceeded that of infants at term with an average figure of 5.0 L/min/M²BSA, approximately 50 per cent in excess of the value reported for fullterm infants (1).

It may thus be concluded that the normal premature infant with respect to central circulatory pattern is characterized by a hyperkinetic circulation as compared to the infant at term. This seems to apply both to the systemic and pulmonary circulation. Other characteristic features of the premature's circulation are the findings of right-left shunt on the atrial level as well as a lower vascular resistance.

The first report involving circulatory data from a large group of premature infants without pulmonary complications is that of Moss et al (15) where the circulatory pattern was analysed from blood pressure and blood gas determinations. These authors concluded that right-left shunting through the ductus arteriosus was uncommon in these infants just as in fullterm infants, and were able to show that systemic but not pulmonary arterial blood pressure was related to the weight of the infant. Although their technique did not allow identification of right-left atrial shunts, the overall venous admixture to systemic blood is approximately of the same magnitude as in the present material.

Relationships between the circulatory pattern of premature infants with and without respiratory distress. The circulatory evaluation of the premature infants with RD suggests that there is considerably lower cardiac output and pulmonary blood flow associated with a higher venous admixture and peripheral resistance. The difference is statistically significant only with respect to pulmonary blood flow ($0.02 < p < 0.05$) a finding which is not surprising in view of the small number of cases studied. It may be argued that the two groups of infants are not directly comparable due to differences in birthweight with the smaller infants usually exhibiting RD. The previous comparison between infants of normal birthweight and the prematures, however, suggests that if a systemic difference is introduced due to difference in birthweight it would be expected to increase rather than decrease the cardiac output in the lighter weight group. It may also be questioned whether the fact that the RD infants were all breathing pure oxygen at the time of the investigation may have introduced a systematic difference in the circulatory pattern. The effect of oxygen on the pulmonary arterial circulation, however, would if anything tend to diminish pulmonary vascular resistance (6) and consequently be responsible for an increase of the pulmonary circulation in the RD infants. It may accordingly be suggested that the overall pulmonary as well as systemic blood flow is smaller in distressed prematures and that both extra- and intrapulmonary venous admixture is increased. It is probably significant that these differences were far most accentuated in the severely affected infant who had systemic and pulmonary perfusion amounting to only ⅓ of the average recorded for non-affected prematures. It is also of interest to note that this infant is the only one who showed a dramatically reduced peripheral circulation with high peripheral

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APPENDIX

Formulae for the calculation of PBF, MVB and VA.

$$PBF = LVO - (R\,L)$$

$$MVB = \frac{(L\,R)\ AAo + (PBF - (L\,R)\ )\ RA}{PBF}$$

$$VA = \frac{(R\,L)\ RA + PBF\ FS - LVO\ AAo}{FS - MVB}$$

Where LVO	=	left ventricular output
PBF	=	pulmonary blood flow
VA	=	venous admixture
L R	=	left right ductal shunt
R L	=	right left foramen ovale shunt
AAo	=	vol % O_2 in ascending aorta
RA	=	vol % O_2 in right auricle
FS	=	vol % O_2 in fully saturated blood
MVB	=	vol % O_2 in mixed venous blood

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From the Department of Paediatrics
(Head: Professor Bo Vahlquist)
University Hospital
Uppsala, Sweden

ECHOENCEPHALOGRAPHY
IN PAEDIATRIC PRACTICE WITH SPECIAL REGARD TO MEASUREMENT OF THE VENTRICULAR SIZE

PART ONE
SOME PHYSICAL ASPECTS OF ULTRASOUND

PART TWO
METHOD AND METHODOLOGICAL DIFFICULTIES

BY
IRENE SJÖGREN

UPPSALA 1967

Translation: MAUD MARSDEN

Indian ink drawings: BIRGIT HÄGGQVIST

Photographs: T. ANNERSTEN & P. E. BARKMAN

Uppsala 1967 Appelbergs Boktryckeri AB

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INTRODUCTION

There has long been a need in paediatrics for a harmless and simple method of recording the intracranial anatomy particularly deviations in size of the ventricular system.

Since the introduction of more active treatment of neuropaediatric patients, for example shunt operations in expansive hydrocephalus, this need has become even more urgent.

An expansion of the ventricular system is not always reflected in variations in cranial size considerable ventricular dilatation may occur at the cost of the cerebral parenchyma without any increase in the cranial circumference, while relatively great cranial enlargement may occur physiologically and without any abnormal widening of the ventricles, for example in premature babies. Only in its more advanced stages can hydrocephalus be diagnosed by transillumination and photographic recording of the abnormalities with this method is a complicated procedure. Cerebral pneumography is the supreme method for detailed study of the ventricular system, but this investigation is time consuming, complicated and not entirely free of risk in infants and small children. Furthermore, the findings at pneumography cannot be repeatedly checked, and after a shunt operation in hydrocephalus it is a dangerous method for follow up examination owing to the risk of gas emboli.

A team study of problems in hydrocephalus has been in progress for several years at the University Hospital in Uppsala (Hadenius et al. 1962, a, b c, Hagberg et al. 1962, Sjögren 1963 Hagberg et al. 1963 Hagberg et al 1964 Sjögren et al. 1964 Sjögren 1964 Sjögren 1965 Granholm & Sjögren 1965 Reuterskiöld & Sjögren 1965 Sjögren et al. 1966, Hagberg & Sjögren 1966, Reuterskiöld & Sjögren 1967). During our discussions on the problems involved in diagnosis and in making decisions for operative procedures, my husband who is a physicist (doctor of technology) expressed his confidence in ultrasonic echo as a diagnostic aid. An ultrasonic apparatus was kindly placed at my disposal by the doctors at the Departments of Neurology and Neurophysiology at this Hospital and my investigations with echoencephalography on hydrocephalic patients began in the autumn of 1962.

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As early as in 1954 Leksell presented his echoencephalographic method (A scan) for studying intracranial anatomy through the intact skull (Leksell 1955). Leksell (1955/56) also pointed out the possibility of diagnosing infantile hydrocephalus by means of echoencephalography This was also discussed by Vlieger & Ridder (1959)

In experimental investigations on autopsy specimens of fresh infantile brains, under conditions as close to normal as possible, Jeppsson (1961) showed it possible to obtain echoes from the interface between brain tissue and cerebrospinal fluid. In another technique Lithander (1961 a) showed that lateral echoes originate in a number of boundary surfaces between brain and cerebrospinal fluid.

Thereafter some investigators (Lithander 1961 b Ford & Ambrose 1963 Schiefer et al 1963 Hemmer 1964 Jacobi & Stephani 1964 West 1964 Umbach & Kley 1965 White et al 1965 Jacobi 1966 Jacobi & Schuch 1966, Lapayoker et al 1966 and others) have considered that echoencephalography is clinically applicable for determining the degree of ventricular dilatation and that it shows "good agreement with cerebral pneumography

However the few more systematic investigations reported, in which echoencephalography has been compared with cerebral pneumography have hardly given convincing evidence that echoencephalography is completely reliable for determining the size of the lateral ventricles in paediatric patients. Thus, Lithander (1961 b) reported 11 children with hydrocephalus in only 8 of whom the lateral ventricle echo was found to be "more laterally situated than normally

From a study of 30 children Mikkelsen (1967) concludes that "only severe central atrophy in children can be diagnosed with certainty"

In the well presented material of Ford & McRae (1966) only three children are included. In a study of newborn infants and adults, Uematsu & Walker (1967) demonstrated enlarged ventricles by echoencephalography in 57 of 64 patients with pneumographically verified ventricular dilatation and also in a further 7 patients who were pneumographically normal West (1967) gave individual data both for the echoencephalographic and the pneumographic values for the widths of the third and lateral ventricles, and concluded that "fairly good agreement was found between the results obtained by the two methods" this conclusion did not pay respect to the fact that differences as high as 47 % were reported between the ultrasonic and roentgenological findings.

However no attempt appears to have been made to analyse the sources of these discrepancies thus, the question is still open as to whether or not it is possible—by a procedure which takes into consideration the special difficulties of evaluating the ventricular size—to rely upon the echoencephalographic findings in an individual paediatric patient.

Preliminary studies (Sjögren 1963, 1964 and 1965) using a method specially adapted for measurement of the ventricular size in infants and children, gave promising results, and comparative studies between this method and cerebral pneumography (to be published) have shown that it is possible to differentiate between normal and dilated ventricular systems in paediatric patients and, further, to determine fairly accurately the size of the lateral ventricles in infantile hydrocephalus. For the purpose of measuring the temporal widths of the ventricles and expressing them in relation to the ultrasonically determined diameter of the head, as indices, I have used the name *echoventriculography (EVG)* so as to emphasize the difference between this echoencephalographic method, developed for infants and children, and the echoencephalographic method used for recording other intracranial structures than the ventricles.

No method of investigation which aims at elucidating the anatomical conditions of the human brain or ventricular system can ever be said to be simple, since in its anatomical construction the brain is such a complex organ. But in comparison with the neuroradiological methods available, the echoencephalographic procedure is extremely simple. However, some small, but most important, practical details and elementary laws of physics regarding the pathways of ultrasound may easily be overlooked; the method requires a knowledge of cerebral anatomy, a sense of form and an ability to think in three dimensions. Furthermore, it has to be kept in mind that human tissues show variations in their acoustic properties at different ages.

This work summarizes some findings from a series of experimental investigations, and presents some physical calculations concerning possible harmful effects of ultrasound in infantile brains, as well as calculations from 700 complete echoencephalographic examinations (see p. 56) in infants and children, with special regard to measurement of the ventricular size. It comprises:

I. some physical aspects concerning ultrasound and infantile osseous and cerebral tissues, and

II. a description of a practical method of examination, and analysis of some sources of error and how they may be eliminated.

Further studies are to be published, comprising:

III. comparative studies, in which the degree of reliability of the presented method is compared with cerebral pneumography with regard to measurements of ventricular size and the diagnosis of cerebral malformations,

IV. an EVG study of normal infants and children, and

V. echoencephalographic follow up studies in patients with hydrocephalus and spina bifida cystica.

In further studies a clinical material will be presented, illustrating some broader aspects of the field of application of this ultrasound technique in paediatrics.

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PART ONE

SOME PHYSICAL ASPECTS OF ULTRASOUND

I GENERAL PROPERTIES

II BIOLOGICAL EFFECTS

III DISCUSSION

IV SUMMARY

PART ONE

SOME PHYSICAL ASPECTS OF ULTRASOUND

SOME PHYSICAL ASPECTS OF ULTRASOUND

I GENERAL PROPERTIES

The suitability of ultrasound for medical diagnostic use is due to the fact that high frequency ultrasound possesses beam properties that are subject to the general laws of radiation. Thus ultrasound can be directed as an almost parallel beam. When an ultrasonic beam is transmitted into the body and encounters an interface between tissues with different acoustic impedance (sound velocity x density), part of the ultrasound is reflected against the surface. Ultrasound reflected in this way gives rise to so called echoes.

Concerning the physical properties and effects of ultrasound reference should be made to the special literature of the subject (Bergman 1954) and also to the works of Hertz (1959) and Jeppsson (1961) on echoencephalography In the following a brief review only is given of some physical data concerning ultra sound of relevance for the diagnostic ultrasonic echo investigations presented in this work.

Ultrasound is defined as sound waves with frequencies lying above the human audible range, i. e. exceeding 18—20 kc/sec. For the examinations to be described here, frequencies of 2 Mc/sec and 4 Mc/sec were used.

As with audible sound waves, ultrasound requires a medium through which it can propagate. This medium may be a gas, a fluid or a solid body

The propagation velocity is dependent on the mechanical properties of the medium, such as density and the interaction between the particles in the medium. On the other hand it is largely independent of the sound frequency Cerebrospinal fluid and cerebral parenchyma have similar mechanical properties to water while bone tissue may be regarded more as a solid body (cf Table I).

Ultrasound, when emitted from a plane surface, proceeds with a slightly divergent beam direction the beam becoming increasingly more parallel with increase in frequency The divergency of the beam is determined by the quotient between the wave length and the size of the radiating surface.

The quotient of the reflected intensity and the incident intensity is called the reflection power and the quotient of the transmitted intensity and the incident intensity is called the transmission power. The determining factors for reflection and transmission are the acoustic impedances of the media, with large differences between these acoustic impedances the reflection power approaches 1 and the transmission power approaches zero. This means that at the interface between, for example, a fluid and a gas or a fluid and a solid body the main part of the incident intensity will be reflected (Table II).

Table II. *Reflection power and transmission power at interfaces between different media (according to Jeppsson 1961).*

Interface between	Reflection power $R = I_R/I_0$	Transmission power $T = I_T/I_0$
air — brain	1	0
brain — bone	0.34	0.66
brain — CSF*	0.0003	0.9997

where I_0 = incident sound intensity
I_R = reflected " "
I_T = transmitted " "
and CSF* = 0.154 mol. saline, equivalent to cerebrospinal fluid.

The reflection of ultrasound is determined by the general laws of radiation; thus the angle of reflection is equal to the angle of incidence. On oblique incidence from a liquid into a solid body the ultrasound may be totally reflected. For example, on passage from water to bone tissue (sound velocity for water: 1504, bone tissue: 3380 m/sec, cf. Table I) reflection may occur if the angle of incidence (β) exceeds 27° ($\sin \beta = \sin 90 \times 1504/3380$, $\beta = 27°$).

Calculations

When a sound wave penetrates a body containing interfaces between different media, part of the incident intensity is absorbed on traversing the material. Furthermore, reflection losses occur at the interfaces. If both the absorption coefficients and the acoustic impedances are known for the different media, the intensity of both the penetrating and the reflecting sound waves can be calculated in every point of the body (cf. Jeppsson 1961, p. 80).

The divergency angle $\varrho = 1.22 \times \frac{\lambda}{D}$

where λ = the wave length and

D = the diameter of a circular radiating surface.

If the frequency and sound velocity are known the wave length can be calculated (frequency x wave length = sound velocity) The wave length is an approximate measure of the expected resolution at a frequency of 3 Mc/sec the wave length in water is approximately $^1/_2$ mm. Consequently the uncertainty in the length determination, using ultrasound is in principle at least of this order

When a wave motion traverses a medium some absorption always takes place. This absorption occurs as expressed in the formula

$$I = I_0 \times 10^{-\frac{\alpha d}{10}}$$

where I_0 = the original intensity

α = the attenuation by absorption in dB per unit of length

d = the distance covered, and

I = the intensity when d has been traversed.

Intensity and amplitude (A) are related by the equation $I = A^2$ by taking the square roots, the laws governing the intensity are applicable to amplitudes. Intensity is usually measured in watt/cm² Intensity divided by the sound velocity (v) gives the radiation pressure $P_{rad} = \frac{I}{v}$ N/cm² (Vigoreux 1966)

When an ultrasonic beam strikes the boundary separating two media with different acoustic impedances (Table I) some of the sound is transmitted and part is reflected at the interface.

Table I *Sound velocity density and acoustic impedance for 0 154 mol. saline equivalent to cerebrospinal fluid ("CSF) brain tissue bone tissue and air of room temperature (according to Jeppsson 1961)*

Medium	sound velocity m/sec	density g/cm³	acoustic impedance g/cm² × sec
CSF"	1504	1.005	1.51×10^5
brain	1515	1.028	1.56×10^5
bone	3380	1.8	6.1×10^5
air	333	0.0012	4.0×10^1

The quotient of the reflected intensity and the incident intensity is called the reflection power and the quotient of the transmitted intensity and the incident intensity is called the transmission power. The determining factors for reflection and transmission are the acoustic impedances of the media; with large differences between these acoustic impedances the reflection power approaches 1 and the transmission power approaches zero. This means that at the interface between, for example, a fluid and a gas or a fluid and a solid body, the main part of the incident intensity will be reflected (Table II).

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bone	3380	1.8	6.1×10^5
air	333	0.0012	4.0×10^1

The absorption losses in the skull (coefficient of absorption (a) at 2 Mc/sec is 4.5 dB/mm (Hüter 1952)) were calculated from the equation

$$\frac{I}{I_0} = 10^{-\frac{a}{10}t}$$

RESULT

Absorption losses $\frac{I}{I_0}$ at a frequency of	Skull thickness (t)	
	1 mm	3 mm
2 Mc/sec	$10^{-0.9}$	$10^{-2.7}$
4 Mc/sec	$10^{-1.8}$	$10^{-5.4}$

The absorption losses in the cerebral parenchyma (coefficient of absorption (a) at 2 Mc/sec is 1.5 dB/cm (Jeppsson 1961)) were calculated from the equation

$$\frac{I}{I_0} = 10^{-\frac{a}{10}d}$$

RESULT $\frac{I}{I_0} = 10^{-2.1}$ at 2 Mc/sec

$\frac{I}{I_0} = 10^{-4.2}$ at 4 Mc/sec

The term cerebral parenchyma includes here the entire distance between the internal surface of the skull and the lateral wall of the contralateral lateral ventricle (d, Fig. 1). Finally the reduction (R) at the interface between the cerebrospinal fluid and the cerebral parenchyma was taken from Table II.

$$\frac{I}{I_0} = R$$

RESULT $\frac{I}{I_0} = 10^{-1.9}$

Results

The results of the calculations are given in Figure 2, where it can be seen that

1) large reductions in intensity occur at the echo producing ventricular surface
2) at frequencies of 4 Mc/sec the absorption losses in the skull and cerebral parenchyma are relatively large.

Since it is the reflections, or echoes that are utilized in diagnostic examinations, it was considered of interest to determine the fraction of the incident intensity leaving the test object after a reflection

The following calculations were therefore performed. A child's head was considered, with a skull thickness (t) of 1 or 3 mm and a distance (d) of 7 cm between the internal surface of the skull and the lateral wall of the contralateral lateral ventricle (Fig 1) Ultrasound at frequencies of 2 Mc/sec or 4 Mc/sec was used in the calculations, the absorption coefficient being proportional to the frequency (Hüter 1952) The threshold for detectable echoes was found to be 10^{-10} of the incident intensity (Jeppsson 1961) for the same type of apparatus as used in this work

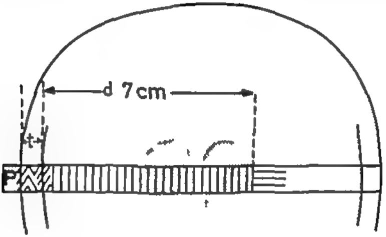

Figure 1 Schematic drawing of the head showing the beam pathway at an echoencephalographic examination.
Ultrasound with an intensity I_0 is transmitted through the probe (P) The ultrasound that is reflected at the lateral wall of the distal lateral ventricle, 7 cm from the internal surface of the skull, and returns to the probe (I), gives a so-called ventricle echo Before the echo can be recorded by the apparatus it is required that at least 10^{-10} of the transmitted ultrasound should return ($\frac{I}{I_0} \geq 10^{-10}$).
Losses of intensity occur by the absorption of ultrasound in the skull (t) and cerebral tissue (d) both on the outward and return passage and also due to reduction at the reflecting surface Other notation as in Fig. 2.

Reflection losses at the two surfaces of the skull (passed twice) were calculated using the transmission power (T) in Table II

$$\frac{I}{I_0} = T^4$$

$$\text{RESULT} \quad \frac{I}{I_0} = 10^{-0.7}$$

The absorption losses in the skull (coefficient of absorption (s) at 2 Mc/sec = 4.5 dB/mm (Hüter 1952)) were calculated from the equation

$$\frac{I}{I_0} = 10^{-\frac{s}{10} 2t}$$

RESULT:

Absorption losses $\frac{I}{I_0}$ at a frequency of	Skull thickness (t) 1 mm	Skull thickness (t) 3 mm
2 Mc/sec	$10^{-0.9}$	$10^{-2.7}$
4 Mc/sec	$10^{-1.8}$	$10^{-5.4}$

The absorption losses in the cerebral parenchyma (coefficient of absorption (s) at 2 Mc/sec = 1.5 dB/cm (Jeppson 1961)) were calculated from the equation

$$\frac{I}{I_0} = 10^{-\frac{s}{10} 2d}$$

RESULT: $\frac{I}{I_0} = 10^{-2.1}$ at 2 Mc/sec

$\frac{I}{I_0} = 10^{-4.2}$ at 4 Mc/sec

The term cerebral parenchyma includes here the entire distance between the internal surface of the skull and the lateral wall of the contralateral lateral ventricle (d, Fig 1) Finally the reduction (R) at the interface between the cerebrospinal fluid and the cerebral parenchyma was taken from Table II

$$\frac{I}{I_0} = R$$

RESULT $\frac{I}{I_0} = 10^{-2.9}$

Results

The results of the calculations are given in Figure 4, where it can be seen that

1) large reductions in intensity occur at the echo producing ventricular surface;
2) at frequencies of 4 Mc/sec the absorption losses in the skull and cerebral parenchyma are relatively large

3) the absorption losses increase greatly with increasing skull thickness

4) at a skull thickness of 3 mm, echoes from the distal ventric surface can be recorded with ultrasonic frequencies of 2 Mc/ c/sec

5) because of the relatively large reduction in ption in the cerebral tissues it should be possible wall of the proximal ventricle w th where the skull thickness is

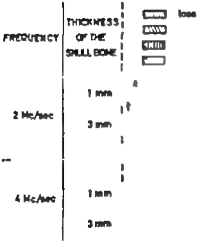

Figure 2 The

sound is detected b

surface (Fig 1). detectable frequency level (thin skulls.

Discussion of

The coeffici data in the lit newborn babies be lower both a lower calciu losses are prob indicated in Fig cular surface wi the differences cerebral parench be recorded.

As with wave movements in general, ultrasonic waves transport energy

The ultrasound used for diagnostic purposes is emitted in short intense pulses separated by resting periods, which gives a low mean intensity

In the reflectoscope used here, the ultrasonic beam has a frequency of 2—4 Mc/sec and a mean intensity of 2.5×10^{-4} watt/cm² which is far below the limit for harmful effects damage was observed in animal tissue experiments at 3.25 watt/cm (Barth & Bülow 1949) before any trauma occurs, the skull has to be damaged, and before this happens skin lesions are manifest, and long before this, pain is experienced (Hüter 1954) a routine echoencephalographic examination may at most give a local increase in temperature of 0 1 C (Jeppsson 1961)

Cavitation will not occur in these frequency and intensity ranges (cf Baldes et al 1958)

In infants, especially newborn babies, the ultrasonic energy penetrates more easily into the cerebral parenchyma than in adults, therefore it is necessary to make sure that even the short intense pulses used in echoencephalography do not produce other harmful effects than heating.

The pulses used have a peak intensity of about 2.5 watt/cm² lasting for about 5 μsec, followed by a resting period of about 5000 μsec (Jeppsson 1961)

Calculations

1 *Thermal effects*

Using the value given by Jeppsson (1961) for temperature increase during a routine examination (3 minutes), i.e. 0 1 C, disregarding any transport of heat from the tissue due to blood circulation, etc., the following calculations were performed.

If the maximum permissible temperature increase is 3 degrees (37°—40 C) the maximum time (t_{max}) for investigation is

$$t_{max} = \frac{3}{0.1} \times 3 = 90 \text{ minutes.}$$

Thus, if an echoencephalographic examination were to take 9 minutes, instead of the 3 minutes in Jeppsson's calculations, the mean intensity could be raised 10 times, to

$$2.5 \times 10^{-4} \times 10 = 25 \times 10^{-4} \text{ watt/cm}^2$$

3) the absorption losses increase greatly with increasing skull thickness

4) at a skull thickness of 3 mm echoes from the distal ventricular surface can be recorded with ultrasonic frequencies of 2 Mc/sec, but not 4 Mc/sec

5) because of the relatively large reduction in intensity due to absorption in the cerebral tissues it should be possible to record echoes from the lateral wall of the proximal ventricle with frequencies of 2 Mc/sec even in cases where the skull thickness is somewhat greater than 3 mm.

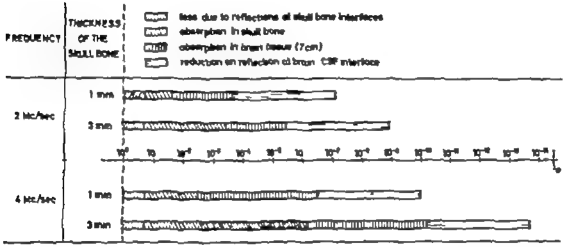

Figure 2 The figure shows the extent to which the intensity (I_0) of the transmitted ultrasound is detected by the echoencephalograph $\left(\frac{I}{I_0}\right)$ after reflection against the distal ventricular surface (Fig 1) The bars give the distribution of the intensity losses. The threshold for detectable echoes is 10^{-9} to 10^{-10} of the incident intensity It can be seen that the higher frequency level (4 Mc/sec) which makes the beam more parallel, can only be used with very thin skulls.

Discussion of the calculations

The coefficients of absorption for the above calculations were obtained from data in the literature based on measurements mainly from adult tissue. For newborn babies and infants the coefficients of absorption may be expected to be lower both for the skull and the cerebral tissue, because of for example, a lower calcium density and lower degree of myelinization The absorption losses are probably lower therefore, for newborn babies and infants than is indicated in Figure 2. On the other hand the reflection capacity of the ventricular surface will be lower with decreased density of the cerebral tissue. When the differences in acoustic impedance between the cerebrospinal fluid and cerebral parenchyma are sufficiently small no ventricular echoes at all can be recorded.

intensity of 2.5 × 10^{-4} watt/cm² or alternatively to increase this intensity 10 times during a 9-minute examination, before pain or any harmful thermal effects will occur·

2. at the high peak intensity (2.5 watt/cm²) repeatedly occurring in the ultrasonic beam, the maximum radiation pressure on, for example, a cell membrane is still negligibly small even under the most unfavourable circumstances, such as total reflection, and will not exceed 3 mm H_2O

3 the kinetic energy of a molecule vibrating in the ultrasonic field is at most 4 × 10^{-24} Ws or 10^{-4} eV this energy is small compared to the kinetic energy of the molecules due to their thermal movements, i.e. 4.3 × 10^{-21} Ws it is also small compared to the bonding energy in the molecule (of the order 1 eV) the quanta of vibrational energy of the molecules (of the order of 10^{-1} eV) and the quanta of rotational energy of the molecules (of the order of 10^{-2} eV)

the acceleration force acting upon an atom in a molecule vibrating at body temperature is more than 10^{13} g this force is shown to be 10^{10} times greater than the acceleration force due to the ultrasonic field, although this latter force has been shown to be as great as 10^3 g.

III. DISCUSSION

The property of ultrasound that makes it particularly suitable for distance measurement is the near parallelism of the beam, which can be propagated through human tissues. Some absorption takes place in the tissues with increasing frequency the absorption increases, but so also does the parallelism of the beam. Frequencies of about 1—4 Mc/sec give sufficiently parallel beams without too much absorption. Ultrasound is reflected at interfaces between tissue structures with different acoustic impedances. The reflections, or echoes, are used for diagnostic purposes. The time taken for the ultrasound to traverse a given distance in a homogeneous medium is directly proportional to the distance.

In order that the reflected ultrasound should return to the same point from which it is transmitted, it must be directed normally to the reflecting surface. When passing in oblique incidence from a soft tissue into bone, ultrasound may be totally reflected even if the angle of incidence exceeds only about 27 (p 15).

At an interface between a solid and a gas the main part of the incident sound intensity will be reflected, due to large differences between the acoustic impedances thus, gas in the path of the beam would cause practically total reflection.

The calculations described on pages 15—18 show that with a sufficiently thin skull it is possible to record echoes from the interface between cerebrospinal fluid and cerebral parenchyma with ultrasonic frequencies of 4 Mc/sec. It is

2 *Mechanical effects*

Using the relation radiation pressure $P_{rad} = \frac{I}{v}$ (p 14) and assuming total reflectance, the pressure on a reflecting surface may be calculated at the peak intensity used (2.5 watt/cm²) and a sound velocity of 1500 m/sec

$$P_{rad} = 2 \times \frac{2.5\ \text{watt/cm}^2}{1500\ \text{m/sec}} \approx \frac{5 \times 10^4\ \text{N m/sec m}^2}{1500\ \text{m/sec}} = 33\ \text{N/m}^2$$

the pressure of 33 N/m² is approximately equal to 3 mm H_2O

3 *Molecular effects*

The thermal energy which corresponds to the heat movement of the molecules is determined by kT where k is the Boltzmann constant ($1\ 4 \times 10^{-23}$ Ws/degree) and T the absolute temperature. At 37°C this energy is equal to

$1\ 4 \times 10^{-23} \times (273 + 37) = 4.3 \times 10^{-21}$ Ws.

At ultrasound frequencies of 1 Mc/sec and 4 watt/cm² a particle in biological tissue oscillating in the ultrasonic field will have a maximal speed of 0.224 m/sec (Hertz 1962) A molecule with a molecular weight of 100 000 i e. 1.7×10^{-22} kg will have a corresponding kinetic energy (E_{kin}) of

$$E_{kin} = \frac{mv^2}{2} = \frac{1.7 \times 10^{-22}\ (0.224)^2}{2} = 4 \times 10^{-24}\ \text{Ws} \approx 10^{-4}\ \text{eV}$$

The quotient between the thermal energy of molecules and the kinetic energy due to oscillations in the ultrasonic field is thus

$$\frac{4.3 \times 10^{-21}}{4 \times 10^{-24}} \approx 1000$$

It has also been shown (Hertz 1962) that the elementary particles in the ultrasonic beam undergo accelerations to the order of 10^3 g (acceleration = amplitude × (angular frequency)²) Using human standards, this figure seems to be *very high but the comparison must be made with accelerations* on an elementary particle level The acceleration force exerted on an atom in a molecule vibrating at absolute zero with an amplitude of 0 1 Å and a frequency of 10^{13} c/sec is

$0\ 1 \times 10^{-10} \times (2\pi \times 10^{13})^2 \approx 4 \times 10^{16}$ m/sec² $\approx 10^{15}$ g

or 10^{10} times greater than the acceleration caused by the ultrasound

Results and discussion

Under the above assumptions the calculations show that

1 it is possible to examine a patient continuously for 90 minutes, at a mean

intensity of 2.5×10^{-4} watt/cm² or alternatively to increase this intensity 10 times during a 9-minute examination, before pain or any harmful thermal effects will occur;

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3. the kinetic energy of a molecule vibrating in the ultrasonic field is at most 4×10^{-44} Ws or 10^{-6} eV; this energy is small compared to the kinetic energy of the molecules due to their thermal movements, i.e. 4.3×10^{-21} Ws; it is also small compared to the bonding energy in the molecule (of the order 1 eV) the quanta of vibrational energy of the molecules (of the order of 10^{-1} eV) and the quanta of rotational energy of the molecules (of the order of 10^{-4} eV)

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Results and discussion

Under the above assumptions the calculations show that

1 it is possible to examine a patient continuously for 90 minutes, at a mean

1) echoes from the interface between cerebrospinal fluid and cerebral parenchyma can be recorded with ultrasound at frequencies of 4 Mc/sec, when the skull bone is about 1 mm thick,

2) echoes from the interface between cerebrospinal fluid and cerebral parenchyma can be recorded with ultrasound at frequencies of 2 Mc/sec, when the skull is about 3 mm thick, and

3) the energy transferred to the tissues during a diagnostic ultrasonic echo examination (A-scan) is considerably below the level at which harmful effects may occur

also seen that the absorption losses increase greatly with increasing cranial thickness Similar calculations were performed by Jeppsson (1961) who showed that in adults reflection occurs against more or less calcified intracranial structures, such as, for example, the pineal body even very minor calcium deposits, which are not visible roentgenologically constitute a good medium of reflection of ultrasound with a minimal reduction of intensity In infants, on the other hand, where the skull is thin *reflection is detected from the interface between the* cerebrospinal fluid and cerebral parenchyma. At such ages where firstly the skull has become so thick that reflection from the interface between cerebrospinal fluid and cerebral praenchyma can no longer be recorded and secondly the intracranial calcifications have not had time to progress to such a degree that the reflection losses are sufficiently small it may be difficult or sometimes impossible to record any echoes at all from intracranial structures (see Jeppsson 1961 *Graph 9*)

It has been shown that a routine investigation using a mean effect of 2.5×10^{-4} W/cm² *may give an increase in temperature* of about 0 1°C, disregarding any transport of energy from the tissue (Jeppsson 1961) while damage has been observed with the use of 3.25 W/cm² (Barth & Bülow 1949) injurious effects are thought to be due to increased temperature, and the calculations on page 20 confirm this theory Only when the ultrasonic motions of the molecules have been randomized i e. transformed into heat, will the molecules obtain kinetic energies high enough to produce harmful effects

For echoencephalography *ultrasound at frequencies of 2—4 Mc/sec, and with* mean intensities of 2.5×10^{-4} watt/cm² is used such intensities cause no sensation of pain or biological trauma On the other hand ultrasound of higher intensities and with continuous or focused radiation can give rise to tissue damage and at lower frequencies the risk of cavitation will increase.

The data concerning absorption and damage, cited above have been obtained from adult tissues Because of the wide safety margins shown to exist, the ultrasonic echo *examination method is safe, even applied to infants, although in*fantile tissue is more vulnerable. However more data concerning infantile tissue would be valuable in order to enable more elaborate calculations for echographic examinations in newborn babies infants and children of different ages.

IV SUMMARY

A short review of some physical properties of ultrasound is presented, and their *importance for* echoencephalographic examinations is discussed.

Calculations made on the basis of data concerning adult tissues, given by other authors, show that

PART TWO

METHOD AND METHODOLOGICAL DIFFICULTIES

I APPARATUS

II PROCEDURE

III ECHOENCEPHALOGRAM AND ECHOVENTRICULOGRAM (EVG)

IV METHODOLOGICAL ERRORS

V COMMENTS CONCERNING THE METHOD

VI SUMMARY

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I APPARATUS

A commercial Siemens Echo-encephalograph, system Krautkramer (type USM 1) modified by Elema Schönander AB, Solna, Sweden (Fig 3) was used for the ultrasonic echo examinations in this study

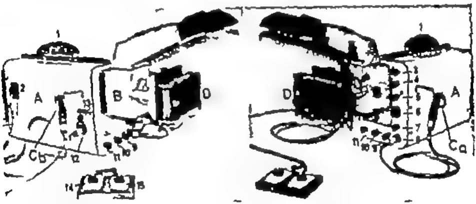

Figure 3 Siemens Echo-encephalograph, system Krautkramer modified by Elema Schönander AB, Solna, Sweden.

(A) Measuring unit. (B) Camera adapter (C_a) Probe cf (8). (C_b) Probe cf. (12). (D) Polaroid Land camera. (1) Handle, facilitating manual transport. (2) Socket for foot switches. (3) Main switch, also used in focusing of electronic ray (4) Horizontal position control. (5) Scale control. (6) Test range switch, which changes the sweep rate so that one sweep can be made to correspond to between 50 and 500 mm tissue. (7) Pulse strength control, which varies the intensity of the ultrasound in 5 stages (for clinical purposes the highest intensity is used). (8) Socket for the cable to probe C_a (used as both transmitter and receiver or alternately as transmitter alone). (9) Depth compensation control, for control of damping of the earlier part of the oscilloscope course; this allows greater amplification of the later pulses which have covered the longest distance in the tissue. (10) Gain control, whereby the amplification can be altered. (11) Scale illumination control. (12) Socket for the cable to probe C_b (receiver in midline control see p 33) (13) Switch for probe C_b for interchange between the echo and transmission methods (14 and 15) Foot switches for inversion and height adjustment, respectively of the tracing on the oscilloscope (which makes possible four different exposures on the same photograph without changing the position of the camera).

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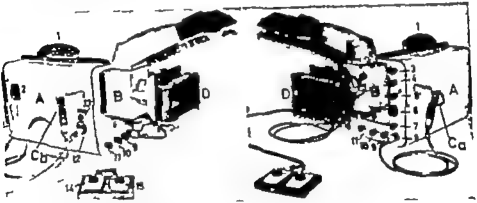

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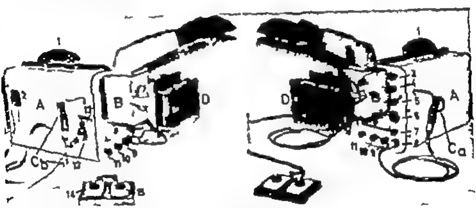

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It consists of a measuring unit (A) with a built in oscilloscope (hidden by the camera adapter (B)) and can be fitted with interchangeable probes (C) and also a Polaroid Land Camera (D) for photographing the oscillogram

Figure 4 shows a block diagram of the system High frequency alternating current from the high frequency generator (see Fig 4.A) is converted to ultra sound by a piezo-electric barium titanate crystal enclosed in the probe (Fig 4-C) The crystal is also able to convert ultrasound to electrical impulses. (A piezo-electric crystal has the property of transforming applied mechanical vibrations (sound) into periodic electrical potential differences between the surfaces of the crystal conversely periodic electrical voltages give rise to mechanical vibrations. These are strongest at the resonance frequencies of the crystal)

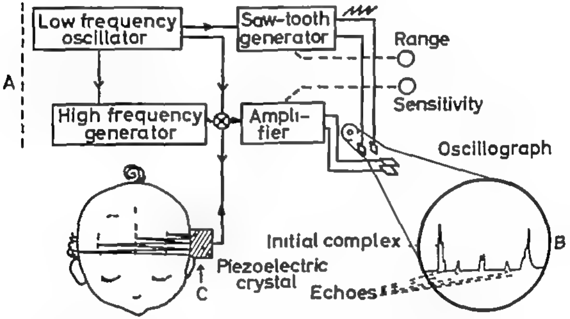


Figure 4 Block diagram of the measuring unit (A) and the picture in the oscilloscope (B) in an echoencephalographic examination of a child with hydrocephalus, where the probe (C) has been applied to the temporal region of the head.

The low frequency generator (see Fig 4.A) functions as a pacemaker and gives pulses with a frequency of 200—250 cycles per second. These pulses influence

1) the high frequency oscillator which together with the crystal gives a transient pulse train lasting about 5×10^{-6} seconds and at a frequency usually between 2 and 4×10^{6} c/sec, i e. 10—20 oscillations the high frequency pulses are heavily damped and decay after about 5 μsec. After this the crystal functions

as a microphone, until the next high frequency pulse train is emitted, i. e. after about 5000 μsec

2) the saw tooth power generator which regulates the X plates of the oscilloscope (Fig. 4-B), giving a horizontal sweep at a frequency of 200—250 cycles per second

3) the amplifier which regulates the input of the Y-plates of the oscilloscope. The low frequency pulses are of such a form that the amplifier is blocked during the period of ultrasound emission. This block is not total, however The strong signal transmitted can be visualized as a complex of deflections in the oscilloscope. This is called the initial complex, and its beginning represents the zero point on the X axis (time-axis).

When the block is removed the amplification is not constant but increases with time. This tends to compensate for the greater damping of those echoes that are returning from deeply situated structures, and thus compensates for their longer absorption distance through the medium

Ultrasound emitted from the probe (Fig. 4-C) strikes a reflecting surface perpendicular to the beam, and returns to the probe, where it is converted by the piezo-electric crystal to electrical impulses, which are then visualized in the oscilloscope as deflections the distance between the initial complex and the upward limbs of these deflections is a measure of the time taken for the ultrasound to pass to and return from the structure which gives the echo If this time (t) and the speed of sound in the medium (v) are known, the distance (d) to the reflecting interface can be calculated ($d = \frac{1}{2} \cdot v \cdot t$). The distance between the beginning of the initial complex and the upward limb of the echo deflection is, *therefore*, proportional to the distance from the site of the probe on the surface of the head to the echo-producing structure. The proportionality factor depends on the setting of the controls for range and scale (Figure 3.(6) and (5))

Probes with a frequency of 4 Mc/sec, and a diameter of 10 mm were used for the examination of infants, and Mc/sec and 10 or 24 mm, respectively for older children.

The probe is constructed so that it can function both as transmitter and receiver (transceiver) for the echo examination. For the midline control examination by the transmission method (Vlieger & Ridder 1959 Lithander 1960, Jeppsson 1961), one probe was used as transmitter and another as receiver by means of a switch (Fig. 3 13) rapid variation between the different methods of examination was possible

Two special test bodies, corresponding to 25 mm and 2.5 mm tissue, respectively are supplied for calibration of the apparatus.

For further details of the coupling system and the apparatus in general, reference should be made to the manufacturer s instructions.

It consists of a measuring unit (A) with a built in oscilloscope (hidden by the camera adapter (B)) and can be fitted with interchangeable probes (C) and also a Polaroid Land Camera (D) for photographing the oscillogram

Figure 4 shows a block diagram of the system High frequency alternating current from the high frequency generator (see Fig 4.A) is converted to ultra sound by a piezo-electric barium titanate crystal enclosed in the probe (Fig. 4-C) The crystal is also able to convert ultrasound to electrical impulses. (A piezo-electric crystal has the property of transforming applied mechanical vibrations (sound) into periodic electrical potential differences between the surfaces of the crystal conversely periodic electrical voltages give rise to mechanical vibrations These are strongest at the resonance frequencies of the crystal)

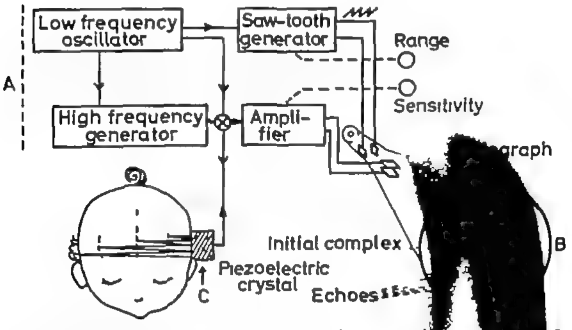


Figure 4 Block diagram of the measuring it (A) and the p cture in th [illegible] echoencephalographic examination of a child with hydrocephalus, where [illegible] applied to the temporal region of the head.

The low frequency generator (see Fig 4.A) functions as gives pulses with a frequency of 200—250 cycles per secon fluence:

1) the high frequency oscillator which, together with the cry sient pulse train lasting about 5×10^{-6} seconds and at a freq tween 2 and 4×10^{6} c/sec, i e. 10—20 oscillations the high fre heavily damped and decay after about 5 μsec. After this the

as a microphone, until the next high frequency pulse train is emitted, i. e. after about 5000 µsec.

2) the saw-tooth power generator which regulates the X plates of the oscilloscope (Fig. 4.B), giving a horizontal sweep at a frequency of 200—250 cycles per second.

3) the amplifier which regulates the input of the Y plates of the oscilloscope. The low frequency pulses are of such a form that the amplifier is blocked during the period of ultrasound emission. This block is not total however. The strong signal transmitted can be visualized as a complex of deflections in the oscilloscope. This is called the initial complex, and its beginning represents the zero point on the X axis (time-axis).

When the block is removed the amplification is not constant but increases with time. This tends to compensate for the greater damping of those echoes that are returning from deeply situated structures, and thus compensates for their longer absorption distance through the medium.

Ultrasound emitted from the probe (Fig. 4·C) strikes a reflecting surface perpendicular to the beam, and returns to the probe, where it is converted by the piezo-electric crystal to electrical impulses, which are then visualized in the oscilloscope as deflections. the distance between the initial complex and the upward limbs of these deflections is a measure of the time taken for the ultrasound to pass to and return from the structure which gives the echo. If this time (t) and the speed of sound in the medium (v) are known, the distance (d) to the reflecting interface can be calculated ($d = \frac{1}{2} \cdot v \cdot t$). The distance between the beginning of the initial complex and the upward limb of the echo deflection is, therefore, proportional to the distance from the site of the probe on the surface of the head to the echo-producing structure. The proportionality factor depends on the setting of the controls for range and scale (Figure 3.(6) and (5)).

Probes with a frequency of 4 Mc/sec, and a diameter of 10 mm were used for the examination of infants, and 2 Mc/sec and 10 or 24 mm, respectively for older children.

The probe is constructed so that it can function both as transmitter and receiver ("transceiver") for the echo examination. For the midline control examination by the transmission method (Vlieger & Ridder 1959, Lithander 1960, Jeppsson 1961) one probe was used as transmitter and another as receiver: by means of a switch (Fig. 3.13) rapid variation between the different methods of examination was possible.

Two special test bodies, corresponding to 25 mm and 2.5 mm tissue, respectively are supplied for calibration of the apparatus.

For further details of the coupling system and the apparatus in general, reference should be made to the manufacturer's instructions.

The apparatus was calibrated and its linearity tested

The *degree of proportionality between the time (X) axis of the oscilloscope and the distances measured* was tested using multiple reflections in the 2.5 mm tissue standard, and the deviation from *linearity was in no place greater than the degree of uncertainty in the individual values,* e g ± 0.3 mm.

In order to determine *whether the horizontal scale remained unchanged when the oscilloscopic tracing was moved vertically* recordings in the four possible oscilloscopic positions were made on one and the same photograph the distance from the beginning of the initial complex to the upward limb of the echo deflection obtained was found to be exactly the same in all positions.

To determine the *numerical relationship between the length of the tissue investigated and the distance in the oscilloscope* (a) *and the distance on the photographic recordings* (b) from the initial complex to the echo deflection for different settings of the apparatus, the following test was performed

Table III *Values obtained from echorecordings from 25 mm tissue standard with the apparatus set at different ranges The setting of the apparatus in other respects is described in the text*

Range according to the apparatus	Measured tissue distance in mm	No. of scale divisions in the oscilloscope (a)	No. of mm on the photograph (b)
100 × 0.5 mm	25	24	40
100 × 1 mm	25	12	20
100 × 2 mm	25	6	10
250 × 0.5 mm	25	10	16
250 × 1 mm	25	5	8
250 × 2 mm	25	2.5	4

A tissue standard corresponding to 25 mm tissue was studied, a probe of 4 Mc/sec and 10 mm diameter being used. Using the horizontal position control, the beginning of the initial complex was placed at the left vertical line in the coordinate grid of the oscilloscope. With the range set at 100 × 0.5 mm, the first echo from the tissue standard was made to coincide with the right margin of the coordinate grid by means of the scale control.

Recordings were then made using all range combinations (Table III)

The distances between the beginning of the initial complex and the different deflections were measured.

The values obtained are given in Table III which shows that the ranges given on the apparatus were in good agreement with the true conditions, since the previous test had proved the linearity of the apparatus.

Thus, it was shown that the apparatus was linear and that its range was in good agreement with the true conditions.

Comments

Provided that the sweep of the apparatus is not altered, calculations can be made from the values in Table III to determine firstly which range is most suitable for the examination of a given length of tissue, and secondly the length of tissue that corresponds to a distance obtained on the photograph. To simplify such calculations in practical work, the following table has been found to be of value (Table IV).

Table IV *Calculations for practical use of the counterparts of different stretches of tissue on the photographic recordings at different measurement ranges of the apparatus as seen in the table the range 100 × 1 mm is most suitable for infants with a small cranial diameter while the range 250 × 0.5 is to be preferred in older children and adults.*

Range according to the apparatus	8 cm on the photograph corresponds to tissue distance of	1 mm on the photograph corresponds to tissue distance of
100 × 0.5 mm	5 cm	0.6 mm
100 × 1 mm	10 cm	1.2 mm
100 × 2 mm	20 cm	2.5 mm
250 × 0.5 mm	12.5 cm	1.6 mm
250 × 1 mm	25 cm	3.1 mm
250 × 2 mm	50 cm	6.2 mm

The photographic recording measured 10 cm (X axis) × 8 cm (Y-axis). It can be seen from Table IV that a range of 100 × 1 mm is most suitable for examinations of infants with a cranial diameter of about 10 cm, while a range of 250 × 0.5 mm is preferable in children with larger heads, and adults. At a range of 100 × 1 mm, 1 mm tissue corresponds to 0.8 mm on the photographic recording and 1 mm on the photograph corresponds to 1.25 mm tissue.

Most other commercially available apparatuses for echoencephalography follow the same principles as those used in this work for details of each individual type of apparatus, reference should be made to the manufacturer's manual of instructions.

II. PROCEDURE

Preparations

For the examination the patient lay in the supine position with the nose pointing straight up towards the ceiling (Fig. 5) Usually the child had recently

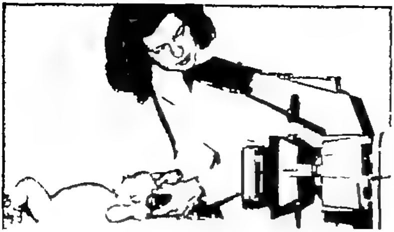


Figure 5 During the examination the patient lay symmetrically in the supine position. The photograph was taken during scanning with the probe held immediately posterior to the test point.

slept and been fed and he was accompanied by his own nurse and if necessary was given a pacifier to suck No sedation was ever required.

Contact media

Liquid paraffin was used as a contact medium between the surface of the probe and the head which was not shaved before the examination

Test point

The probe was, as a rule, held 2—3 cm above and 1—3 cm anterior to the external auditory meatus (test point Tp Fig 6) The probe was directed towards the corresponding point on the opposite side of the head.

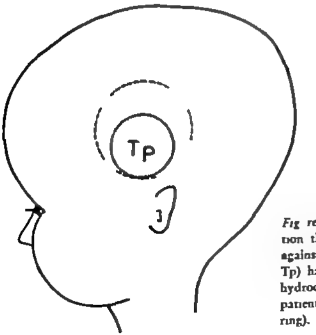
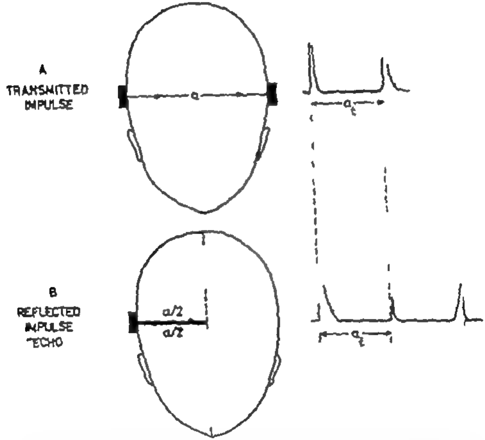


Fig re 6 In an echoventriculographic examination the central point of the site on the head against which the probe is placed (test point, Tp) has to be sought with w der region in hydrocephalic pat ents (dotted ring) than patients with normal cra ial d ameters (whol ring).

Midline control

The examination was begun with a midline control (see p. 29) whereby ultrasound was transmitted by one probe and detected by another placed congruently on the opposite side of the head (Fig. 7) the surfaces of the two probes were held parallel. The oscillogram at the midline control examination was photographed.



F g re 7 Midline control The time taken for ltrasound to pass from the one probe (black) to the other ( ) by the transmission method (A) is equal to that taken for it to pass from one probe to he geometrical midline (dotted) and back again to the same probe, as in the echo method (B). The distanc measure of the same time on the oscilloscope screen.

Echo examination

The echo examination was performed from both the right and left sides, from the same points at which the probes were placed for the midline control exami

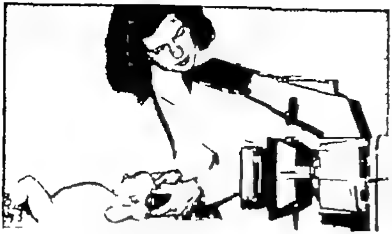


Figure 5 During the examination the patient lay symmetrically in the supine position. The photograph was taken during scanning with the probe held immediately posterior to the test point.

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Liquid paraffin was used as a contact medium between the surface of the probe and the head which was not shaved before the examination.

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The probe was, as a rule, held 2—3 cm above and 1—3 cm anterior to the external auditory meatus (test point Tp, Fig. 6). The probe was directed towards the corresponding point on the opposite side of the head.

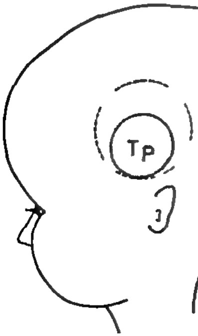

Figure 6. In an echoventriculographic examination the central point of the site on the head against which the probe is placed (test point, Tp) has to be sought within a wider region in hydrocephalic patients (dotted ring) than in patients with normal cranial diameters (whole ring).

Midline control

The examination was begun with a midline control (see p. 29), whereby ultrasound was transmitted by one probe and detected by another placed congruently on the opposite side of the head (Fig. 7) the surfaces of the two probes were held parallel. The oscillogram at the midline control examination was photographed.

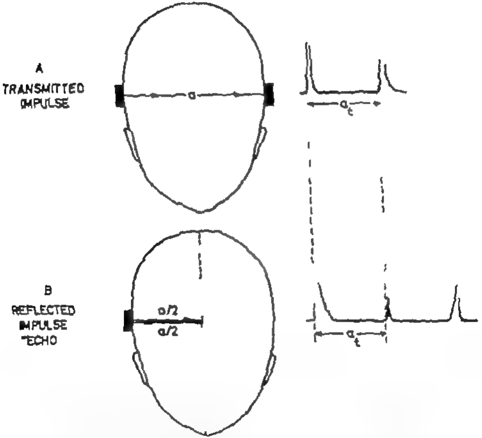

Figure Midline control. The time taken for ultrasound to pass from the one probe (black) to the other ( ) by the transmission method (A) is equal to that taken for it to pass from one probe to the geometrical midline (dotted) and back again to the same probe, as in the echo method (B). The distance measure of the same time on the oscilloscope screen.

Echo examination

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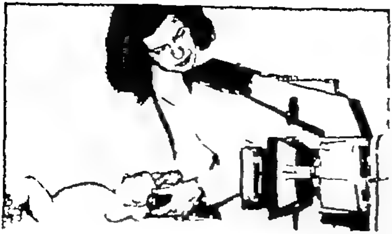


Figure 5 During the examination the patient lay symmetrically in the supine position. The photograph was taken during scanning with the probe held *immediately posterior to* the test point.

slept and been fed, and he was accompanied by his own nurse and if necessary was given a pacifier to suck No sedation was ever required

Contact media

Liquid paraffin was used as a contact medium between the surface of the probe and the head which was not shaved before the examination.

Test point

The probe was, as a rule, held 2—3 cm above and 1—3 cm anterior to the external auditory meatus (test point Tp Fig 6) The probe was directed towards the corresponding point on the opposite side of the head

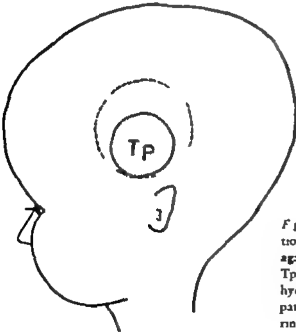


Figure 6 In an echoventriculographic examination the central point of the site on the head *against which the probe is placed* (test point, Tp) has to be sought within a wider region in hydrocephalic patients (dotted ring) than in patients with normal cranial diameters (whole ring)

Midline control

The examination was begun with a midline control (see p 29) whereby ultrasound was transmitted by one probe and detected by another placed congruently on the opposite side of the head (Fig. 7) the surfaces of the two probes were held parallel. The oscillogram at the midline control examination was photographed.

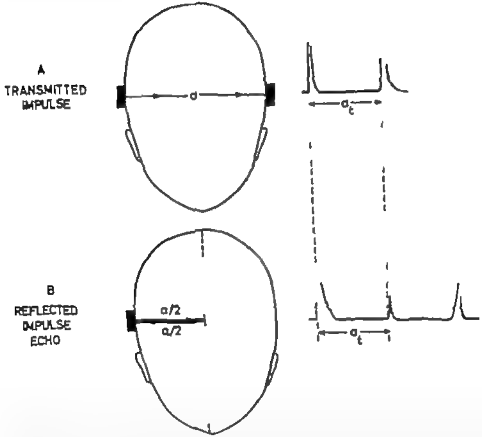


Figure 7 Midline control. The time taken for ultrasound to pass from the one probe (black) to the other ( ) by the transmission method (A) is equal to that taken for it to pass from one probe to the geometrical midline (dotted) and back again to the same probe, as in the echo method (B). The distance a_t is *measure of the same time on the oscilloscope screen.*

Echo examination

The echo examination was performed from both the right and left sides, from the same points at which the probes were placed for the midline control exami

nation At the echo examination the oscillogram was followed while the probe was moved slightly against the surface of the head and the gain control of the apparatus was manoeuvred The bottom echo midline echo echo-free zones and lateral ventricle echoes were identified on the oscilloscope screen When the midline echo and the distal lateral ventricle echo appeared to rise at their steepest angles from the time axis, the oscillogram was photographed

Lateral ventricle echo

The lateral ventricle echo was defined as that echo which delimited laterally an echo-free zone, which in turn was divided medially by the midline echo a check was made that the echo-free zone remained free of echoes even at maximal amplification In cases where the midline echo and lateral ventricle echoes could not be identified simultaneously from the position used for the *midline control examination* a new *midline control recording* was made from the site at which these echoes could be detected

"Scanning"

After each echo examination as described above the tracing in the oscilloscope was observed while the probe was being moved along the sides of the head and also while the probe was held in a fronto-occipital and occipito-frontal direction This part of the investigation was called "scanning

On scanning

1) the *identity of the midline echo* was verified a midline echo usually pulsating can be recorded over a considerably larger area of the head in children than in adults (Jeppson 1960 Lithander 1961)

2) any *asymmetries anterior or posterior to the test point* were recorded photographically

3) *the width of the midline echo* was checked while the probe was moved 1—2 cm forwards and downwards from the test point in cases where the configuration and/or the width of the midline echo was then found to be altered, a fourth recording was photographed corresponding *to the region of projection of the third ventricle*

4) *the extent of an echo-free zone from the ventricular system was noted* if its breadth was not considered to correspond to that of a harmonically dilated ventricular system the deviating oscillogram was photographed

5) *any echo-free zones suspected to be of other origin than the ventricular system* which aroused suspicion of porencephaly or cyst of the fourth ventricle, for example were recorded photographically

6) any *atypical repeatedly recurring echoes* which aroused suspicion of for example a cyst wall or tumorous calcification were recorded photographically

Other recordings

When photographic recordings were made as in points 2, 4 5 and 6 a midline control determination was also made, when possible, between the congruent points on each side of the head, from which the echoes had been recorded.

In echo examinations performed in a fronto-occipital and/or occipito-frontal direction, the probe was held on the right and left side of the forehead and/or the occipital region, respectively for midline control determinations in the longitudinal plane the probes were held in the centre of the forehead and centrally over the most prominent part of the neck, thus corresponding to the largest longitudinal cranial diameter In all cases where such extra recordings were made, the position and direction of the probe at the examination was denoted by arrows on a sketch of the head, drawn for each individual patient.

III. ECHOENCEPHALOGRAM AND ECHOVENTRICULOGRAM (EVG)

Definitions

Echoencephalogram

By echoencephalogram is meant one single reflection pattern recording (Leksell 1955 56) Depending on the thickness of the skull and the position of the probe an echoencephalogram consists of deflections (echoes) due to the reflection of the ultrasound *from the skull and different intracranial structures.*

Echoventriculogram (EVG)

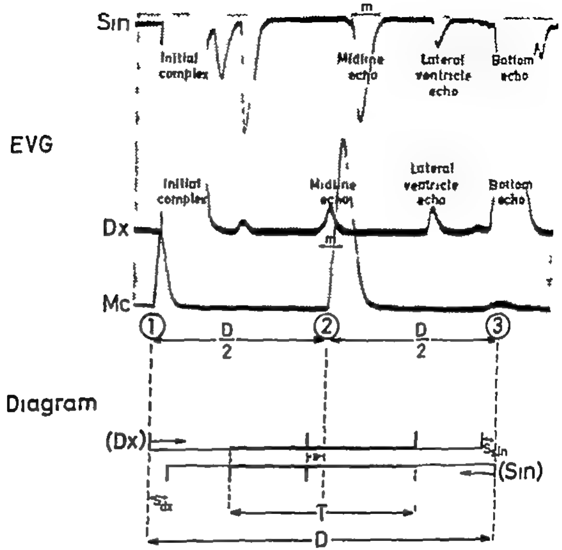
By echoventriculogram (EVG) is meant a photographic recording of a midline control between the right and left test points together with echoencephalograms showing the midline echo (see 3) p. 34) bottom echo and distal lateral ventricle echo from the right and left test points.

Graphical representation and index calculations of EVG

In the following the methods of graphical representation and index calculations are described, and the reader is referred to Figure 8.

The grey field in Figure 8 shows a model EVG, in which Mc at the bottom denotes the midline control recording, Dx an echoencephalogram from the right test point, and Sin an echoencephalogram from the left test point.

Each recording begins with the *initial* complex the measurements are made from the beginning of this complex (the thin upward limb at the end of the first straight part on the time axis) to the upward limbs of deflections in the different recordings.



Indices

Lateral venticular index $= I = T/D$

Midline index $= I_m = m/D$

Midline deviation index $= I_x = x/D$

Superficial structure index $= I_s = s/D$

Figure 8 An echoventriculogram (EVG) within the gray field, where Mc represents the midline control Dx an echoencephalogram from the right and Sin one from the left test point. The graphical representation and index calculations are explained in the text.

Midline control recording (Mc)

From the initial complex and the upward limb of the single deflection in Mc (EVG, Fig. 8) vertical parallel dotted lines are drawn downwards, marked 1 and 2 the distance between 1 and 2 is called midline control distance and marked $\frac{D}{2}$ The double midline control distance is also marked with a vertical line (3) parallel with the vertical lines 1 and 2. The double midline control distance (D Diagram, Fig. 8) corresponds to the outer temporal diameter of the patient's head.

In the diagram obtained (Diagram, Fig. 8) the three dotted vertical lines correspond to

(1) the right external head surface

(2) the geometrical midline

(3) the left external head surface.

In the diagram two horizontal, parallel thin lines are drawn, called echo lines the upper one representing the time axis of the echoencephalogram from the right testpoint (Dx) and the lower one that from the left (Sin).

The initial complex from Dx (EVG, Fig. 8) is indicated by a short vertical line at dotted line 1 (corresponding to the right external head surface) the initial complex from Sin (EVG Fig. 8), is indicated by a short vertical line at dotted line 3 (corresponding to the left external head surface) the arrows from these initial complex indications show the direction of the beam of the transmitted ultrasound.

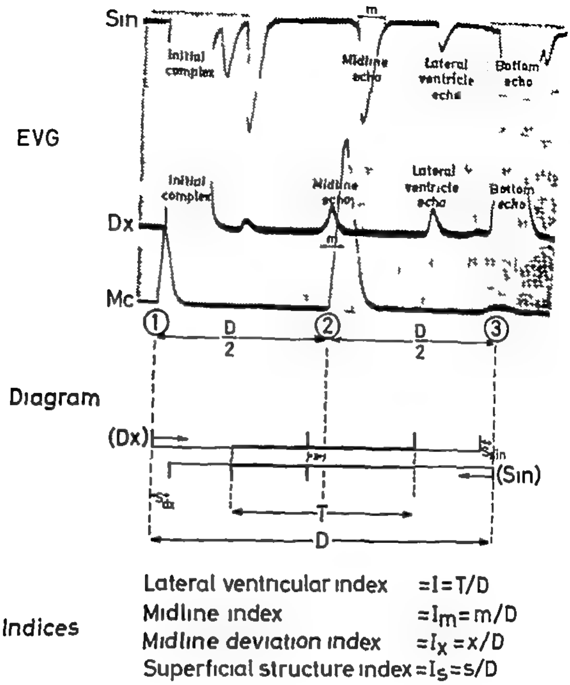
Echoencephalogram (Dx and Sin)

From the echoencephalogram from the right test point (Dx, EVG Fig. 8) the distances from the initial complex to the midline echo, the distal lateral ventricle echo and the bottom echo are measured. Also the distances from the initial complex to the beginning and the end of completely echo-free zones are measured. The distances measured are then transferred to the diagram the distances from the initial complex to the respective echoes are indicated by short vertical lines at the echoline (Dx), and echo-free zones are indicated by thick horizontal lines, the distances are marked in the diagram from left (vertical line 1) *to* right.

From the echoencephalogram from the left test point (Sin, EVG Fig. 8) the distances corresponding to those from Dx are measured, and transferred to the diagram these distances are marked at the echoline (Sin) from right (vertical line 3) to left.

Lateral ventricle transversal (T)

The distance between the indication (Diagram, Fig. 8) for the distal lateral ventricle echo from Dx (to the *right in* the diagram) and that from Sin (to



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In the diagram obtained (Diagram, Fig. 8) the three dotted vertical lines correspond to:

(1) the right external head surface
(2) the geometrical midline
(3) the left external head surface.

In the diagram two horizontal parallel thin lines are drawn, called echo lines the upper one representing the time axis of the echoencephalogram from the right testpoint (Dx) and the lower one that from the left (Sin)

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From the echoencephalogram from the right test point (Dx, EVG Fig 8) the distances from the initial complex to the midline echo, the distal lateral ventricle echo and the bottom echo are measured. Also the distances from the initial complex to the beginning and the end of completely echo-free zones are measured. The distances measured are then transferred to the diagram the distances from the initial complex to the respective echoes are indicated by short vertical lines at the echoline (Dx) and echo-free zones are indicated by thick horizontal lines, the distances are marked in the diagram from left (vertical line 1) to right.

From the echoencephalogram from the left test point (Sin, EVG Fig. 8) the distances corresponding to those from Dx are measured, and transferred to the diagram these distances are marked at the echoline (Sin), from right (vertical line 3) to left.

Lateral ventricle transversal (T)

The distance between the indication (Diagram, Fig. 8) for the distal lateral ventricle echo from Dx (to the right in the diagram) and that from Sin (to

the left in the diagram) was measured and has been called the ventricle transversal (T) this is assumed to correspond to the total breadth of the lateral ventricles in the frontal plane.

Lateral ventricle index (I)

The combined breadths of the lateral ventricles (T) is expressed in relation to the temporal diameter (D Fig 8) as a lateral ventricle index $I = T/D$

Midline index (Im)

The width of the midline echo (m) was measured on the echograms (EVG, Fig 8) and expressed in relation to D as a midline index $Im = m/D$

Superficial structure index (Is)

The indications for the bottom echo from echoencephalograms Dx and Sin (EVG Fig 8) are situated near the vertical lines 3 and 1 respectively in the diagram the distances between these indications and the nearest vertical lines (s_{sin} and s_d in the Diagram Fig. 8) were measured and expressed in relation to D as superficial structure indices

$Is_d = \frac{s_{dx}}{D}$ is an expression for the thickness of the superficial structures at the right and $Is_{sin} = \frac{s_{sin}}{D}$ an expression for the corresponding thickness at the left temporal region of the patient s head when s_{dx} is equal to s_{sin} the superficial structure is simply expressed as $Is = \frac{s}{D}$

Midline deviation (x)

In the diagram (Fig 8) the indications for the midline echoes from Dx and Sin are positioned on the same vertical line In cases where this vertical line does not coincide with the geometrical midline, the midline deviation (x) is measured as the distance between the geometrical midline (vertical line 2) and the marks representing the midline echoes if the midline echo marks from echoencephalograms Dx and Sin respectively are not exactly on the same vertical line in the diagram the distance from vertical line 2 to a midline drawn half way between the respective midline echo marks is called x.

Figure 9 Schematic pneumogram compared with enlarged, schematic EVG where Mc = the midline control, Dx the echoencephalogram from the right test point and Sin an inverted echoencephalogram from the left test point.
The positions of the lateral ventricle echoes correspond to the lateral interfaces of the lateral ventricles, and the echo-free zones to the breadths of the lateral ventricles seen in the pneumogram. The position of the cerebral parenchyma in the pneumogram corresponds to small echoes, called parenchymal echoes, in the echoencephalograms (between the lateral ventricle echoes and the bottom echoes)

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$Is_{d} = \frac{s_{dx}}{D}$ is an expression for the thickness of the superficial structures at the right, and $Is_{sin} = \frac{s_{sin}}{D}$ an expression for the corresponding thickness at the left temporal region of the patient's head when s_{dx} is equal to s_{sin} the superficial structure is simply expressed as $Is = \frac{s}{D}$

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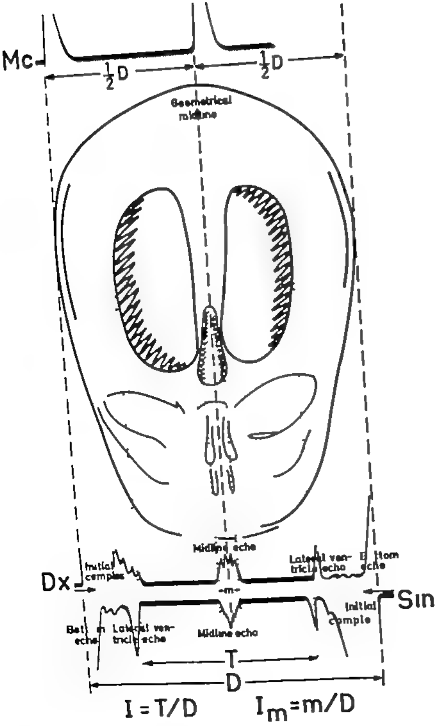

Mc
½D
½D
Geometrical midline
Midline echo
Initial complex
Lateral ventricle echo
Dx
Sin
m
Initial complex
Lateral ventricle echo
Midline echo
T
D
I = T/D
I_m = m/D

Any midline deviation is either expressed in relation to D as a midline deviation index $Ix = \frac{x}{D}$ or is given in millimeters (calculated from Table IV p. 31).

By multiplying the respective indices by 100 expressions are obtained for the combined breadths of the ventricles, the width of the midline echo, the thickness of the superficial structures and the magnitude of the midline deviation in per cent of the cranial diameter in the frontal plane.

Figure 9 shows a schematized pneumogram compared with an enlarged EVG where Mc at the top of the figure denotes a midline control recording, Dx an echoencephalogram from the right test point and Sin an inverted echoencephalogram from the left test point.

Echo-free zones

It can be seen in the figure that the echo-free zones, which are divided medially by the midline echo and delimited laterally by the lateral ventricle echo, correspond to the lateral ventricles in the pneumogram

Parenchymal echoes

Between the lateral ventricle echo and the bottom echo, a series of minimal echoes were noted on both sides, corresponding to the position of the cerebral parenchyma in the pneumogram in the following such echoes will be referred to as parenchymal echoes"

Graphical representation of other recordings

Using the midline control distance of the EVG (Fig 10 A) and one or more midline control distances photographed at other recordings (Fig 10 B) diagrams have been constructed demonstrating three projections of the head in individual cases. A free drawing of the contours of the head is then made with the double midline control distances as diameters (Figs. 10 & 11) the contours being based in all cases on sketches of the shape of the child's head which were made at the time of the examination

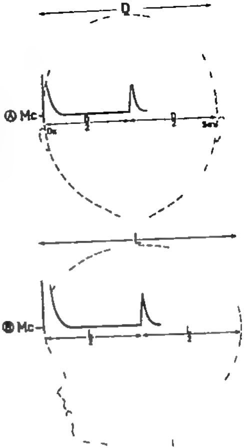
Representation of ultrasound pathway echoes and echo-free zones

Within the constructed dotted lines described above, representing the external contour of the head the echoencephalograms are marked with thin lines (echolines) and the pathway of the ultrasound from the surface of the head is marked with an arrow as in the EVG diagrams. Ideal echoes (see p 45) are marked on the echoline by lines at right angles to it, echo-free zones (which have remained echo-free even at maximal amplification of the apparatus) are marked by heavy lines along the echoline, while the thin echoline represents the extent of the initial complex and echo-producing zones.

Figure 10. Principle for construction of external contour of the head, with the guidance of photographic recordings of midline controls (Mc) according to the transmission method.

A. Mc in temporal region immediately above and anterior to the external auditory opening; the double midline control distance corresponds to the cranial diameter in the frontal plane (D).

B. Mc in fronto-occipital direction; the double midline control distance corresponds to the greatest longitudinal cranial diameter (L).



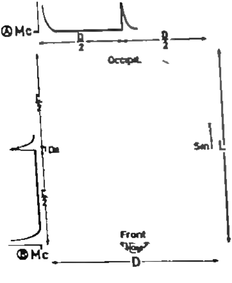


Figure 11. Using D and L according to A and B, respectively, in Fig. 10, together with sketches of the shape of the child head, the external contour of the head, seen from above, has been constructed.

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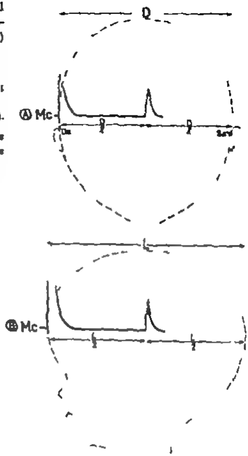

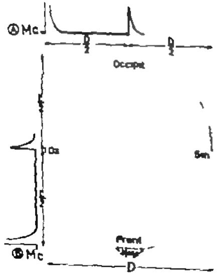

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cephalic patient, where ideal lateral ventricle echoes (see p 45) were obtained.

The index in one and the same patient was determined 17 times in the same number of echoventriculograms, which had been obtained during a period of 30 minutes by 17 independent recordings, where the probe was laid aside between each new recording. The individual index values obtained at these 17 determinations were as follows:

0.67 0.69 0.70 0.70 0.70 0.71 0.67 0.69 0.70 0.70 0.71 0.71 0.67 0.69 0.70 0.70 0.71

The mean value was thus 0.695

Elementary statistical treatment followed, using the equation

$$S = \sqrt{\frac{\sum_{4} \Delta^2}{n-1}} \text{ where}$$

S = the standard deviation of the individual determination,

$\sum_{4} \Delta$ = the sum of the square of the deviations from the mean value and

n = the number of determinations

RESULT Mean value for the 17 determinations = 0.695

S = 0.014

This shows that at this index level the error is about ± 2 %.

IV METHODOLOGICAL ERRORS

For several reasons, echoencephalographic examination of paediatric patients is more difficult than that of adults. For reliable results it is obviously essential that the examiner is absolutely familiar with his apparatus and possesses thorough knowledge of the anatomy of those structures to be investigated. Furthermore, knowledge of the possible sources of error is required, as these may otherwise ruin the results.

Probe against head surface with small curvature radius

The probes which have been available until recently for medical diagnostic use were not actually constructed for this purpose, but for industrial technical work. The surface of the probe is thus completely flat and circular and does not therefore follow the contours of the small, rounded head of an infant.

Since the transmitted effect is directly proportional to the effective radiating surface (cf p. 14), the amplitude of the recorded echoes will be low in cases where the probe surface is only tangential to the surface of the head, which may occur especially in examinations of newborn babies.

On account of the fact that the transmitter is not ideal, i.e. that it does not emit identical waves from each and every point of its surface, gross ampli

Summing up according to the EVG

A Recordings

1 Midline control
2 Echoencephalogram from the right temporal area.
3 Echoencephalogram from the left temporal area.

B Graphical representation

1 A diagram is constructed where the double midline control distance corresponds to the outer diameter of the head (D) in the frontal plane three vertical parallel lines symbolize from left to right the right head surface, the geometrical midline and the left head surface, respectively

2 The distances measured in the right echoencephalogram, from the initial complex to the midline echo, distal lateral ventricle echo and the bottom echo respectively are transferred to the diagram and marked in from left to right.

3 The distances measured, in the left echoencephalogram, from the initial complex to the midline echo distal lateral ventricle echo and the bottom echo respectively are transferred to the diagram and marked in from right to left.

C Index calculations

1 The ventricle transversal (T) (between the two marks for the lateral walls of the distal lateral ventricles in the diagram) is measured and expressed in relation to D as a lateral ventricle index $I = T/D$

2 The breadth of the midline echo (m) is measured and expressed in relation to D as a midline index $Im = m/D$

3 The distance (s) between the marks for the bottom echoes on each side and the adjacent vertical line in the diagram is measured and expressed in relation to D as a superficial index $Is = s/D$

4 The distance (x) between the marks for the midline echoes and the geometrical midline in the diagram is measured and expressed in relation to D as a midline deviation index $Ix = x/D$

Accuracy and standard deviation in lateral ventricle index determinations

In order to determine the accuracy of the lateral ventricle index determination the standard deviation for index determination was studied in a hydro-

cephalic patient, where ideal lateral ventricle echoes (see p. 45) were obtained.

The *index in one and the same patient* was determined 17 times in the same number of echoventriculograms, which had been obtained during a period of 30 minutes by 17 independent recordings, where the probe was laid aside between each new recording. The individual index values obtained at these 17 determinations were as follows:

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The mean value was thus 0.695.

Elementary statistical treatment followed, using the equation

$$S = \sqrt{\frac{\sum_1 \Delta_i}{n-1}} \text{ where}$$

S = the standard deviation of the individual determination,

$\sum_1 \Delta$ = the sum of the square of the deviations from the mean value and

n = the number of determinations.

RESULT: Mean value for the 17 determinations = 0.695

$S = 0.014$

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On account of the fact that the transmitter is not ideal, i.e. that it does not emit identical waves from each and every point of its surface, gross ampli-

tude distortion in the near field may occur this contributes towards the difficulties in obtaining echoencephalograms with ideal echoes in examinations of newborn babies, with small cranial diameters, where this "dangerous near" field region coincides with the distance to be studied. These difficulties are reduced if a probe with a small transmitter diameter is used and also if the echoencephalographic picture representing the distal, and not the proximal half of the head is evaluated in accordance with the EVG evaluation.

Contact between surface of probe and object of examination

For satisfactory results it is necessary for good contact to be obtained between the probe surface and the surface of the examination object, and the contact

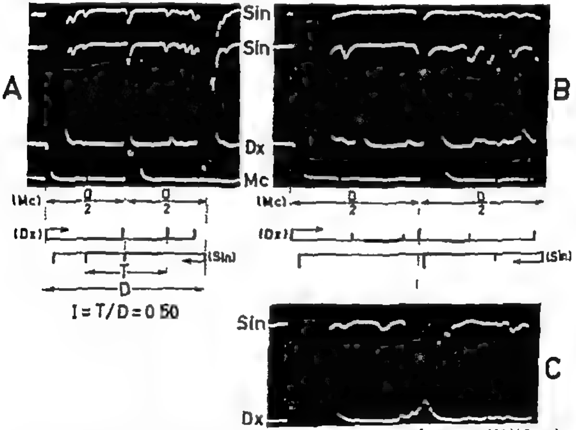

Figure 12 A. EVG of an infant with moderate hydrocephalus. (Range of apparatus 100 × 2 mm) Notation, diagrammatic representation and calculation of indices as in Figure 8. Between the midline echoes and the lateral ventricle echoes are noted broadened echo-free zones in all echoencephalograms.
B and C. Recordings on the same patient, photographed 10—20 seconds later than A. (Range of apparatus 250 × 0.5 mm) In B a series of irregular non-reproducible echoes (artefact echoes) are noted instead of the distal echo-free zones and lateral ventricle echoes. In C the ordinary echoencephalogram is totally replaced by artefact echoes.

medium between these two surfaces must be thin enough to be regarded as negligible when measuring the distances. If the probe is pressed *hard against* the surface of the examination object, and the pressure then released somewhat, the contact medium can be pressed away and air can pass in between the two surfaces, which will give rise to total reflection of ultrasound (see p. 15).

In attempts at seeking "ideal" lateral ventricle echoes (see below) in infants, the probe must be rocked and moved slightly over the test point; in doing this small air bubbles may easily pass in to the layer of liquid paraffin and cause so-called artefact echoes, which may be projected on to the oscilloscopic tracing and give rise to erroneous interpretation of the echoencephalogram.

Figure 12 A shows a *lege artis* EVG examination on a patient with moderate hydrocephalus. Figure 12 B shows an EVG examination on the same infant, after the probe had been rocked very slightly on the surface of the head, and was then again held still against the same point as before; the layer of contact medium between the two surfaces remained unchanged in thickness, but through the transparent protective ring a few air bubbles, the size of a pin-head, were seen under the contact surface of the probe. A series of confluent, non-reproducible echoes are now superimposed on the ordinary echoencephalogram tracing, and are seen over the site of the distal echo-free zone (cf. recording A). Such artefact echoes may be mistaken for parenchymal echoes, and echo-free zones due to dilated ventricles may be overlooked. Figure 12 C shows another recording in which the ordinary echoencephalogram tracing is almost obliterated by artefacts.

Positioning of the probe in relation to the position of the reflecting surface

For accurate distance measurement with the ultrasonic echo method, the surface of the probe should run parallel with the reflecting surface. When this criterion is fulfilled, so-called *ideal echoes* are obtained, where the upward limb of the deflection is thin and rises practically at right angles to the time axis of the oscilloscopic tracing (Fig. 13:I).

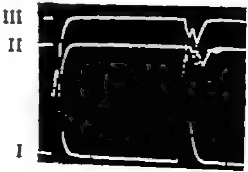

Figure 13 I Ideal echo: reflecting surface parallel to the surface of the probe.
II and III Wide echoes: reflecting surface positioned at an angle of about 8° to the surface of the probe.
Five camera exposures are made for each recording.

If the probe is held at an angle to the reflecting surface, broad, multi peaked echoes may be obtained. Figure 13 II and III show such echoes in experiments in which this angle was about 8

Even with a relatively moderate angle between the surface of the probe and the reflecting surface, total reflection (cf p 15) can occur on return of the ultrasound through the bone.

Position of the head

At the EVG examination the position of the infant's head is of importance for the results fairly considerable intracranial displacements may occur if for example, a hydrocephalic patient is turned from the supine to the lateral position Therefore in order to obtain comparative results the same position should be used for all examinations, the most suitable being the supine position.

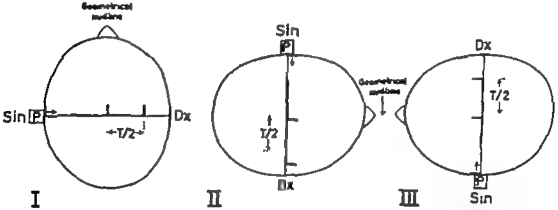

Figure 14 Schematic presentation of echoencephalograms with regard to midline echo and distal lateral ventricle echo in an infant with moderate hydrocephalus, recorded from the left test point (P = the probe) The figure shows displacement of the midline echo and the lateral ventricle echo in the right lateral position (II) as well as minimal displacement of the midline echo in the left lateral position (III) compared to the supine position (I)

Figure 14 shows schematically the results obtained with respect to the right lateral ventricle, on examination of an infant with moderate hydrocephalus. On examination in the supine position (I) the lateral ventricle index was calculated to be 0.60. With the right lateral position (II), fairly considerable deviation of the right lateral ventricle echo was noted, and a lateral ventricle index of 0.85 was obtained; in addition, slight deviation of the midline echo to the right was observed. When the infant was examined in the left lateral position (III) (with its head resting against the probe (P)) no deviation of the right lateral ventricle echo was noted, but slight deviation of the midline echo to the left was seen.

Geometry concerning the ultrasound pathway

The human ventricular system is complicated both in form and distribution (Fig. 15), and its marginal surfaces run parallel with the cranial surface only sporadically.

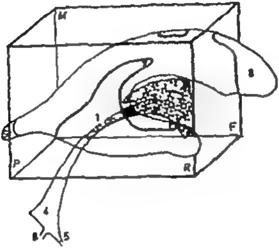

Figure 15 Schematic illustration of the normal human ventricular system, showing its complicated geometrical configuration. The greater part (grey) of the ventricular system is enclosed in an imaginary plexiglass box (light grey field = right lateral ventricle, dark grey field = 1 aqueduct of Sylvius, 2 foramen of Monro, 3 third ventricle).
The dorsal wall (M) of the plexiglass box represents the medial plane of the head. The aqueduct (1) thus cuts through its posterior inferior corner and the fourth ventricle (4) with the foramen of Luschka (5) to the right and the foramen of Magendie (6) in the midplane, lies outside the plexiglass box.
The proximal wall (R) is tangential to the right wall of the lateral ventricle's cella media (7), against which ultrasound is usually reflected on EVG. The frontal horn of the lateral ventricle (8) protrudes through the front wall (F) more medially than does the occipital horn (9) through the posterior wall (P). The temporal horn (10) projects through the box both frontally and laterally (i.e. through walls P and R).

In echoencephalographic examination from the test point, the ultrasonic beam can be made to fall at right angles to the marginal surfaces of the lateral ventricles at the level of the cellae mediae, whereby the beam meets both convex and concave, more or less spherical surfaces with varying radii. Thus for adequate evaluation of an echoencephalogram, with special regard to the ventricular system, consideration must be taken of the geometrical conditions and physical laws of radiation.

An attempt to explain the influence of the curvature radius of a reflecting spherical surface is made in Figure 16.

If the probe is held at an angle to the reflecting surface, broad, multi peaked echoes may be obtained. Figure 13:II and III show such echoes in experiments in which this angle was about 8°

Even with a relatively moderate angle between the surface of the probe and the reflecting surface, total reflection (cf p 15) can occur on return of the ultrasound through the bone.

Position of the head

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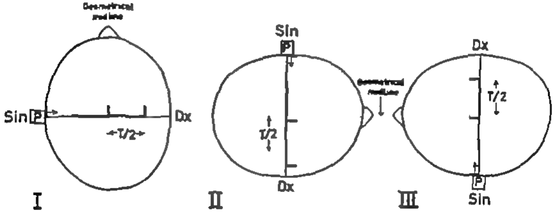

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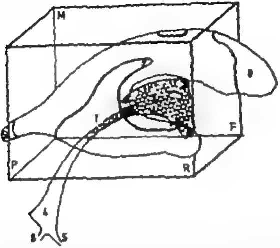

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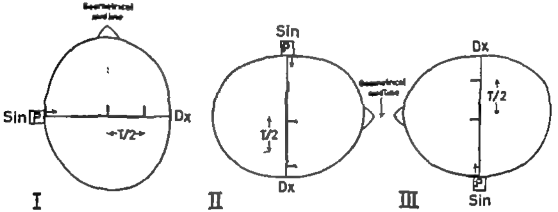

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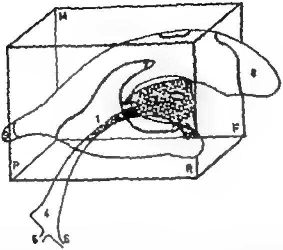

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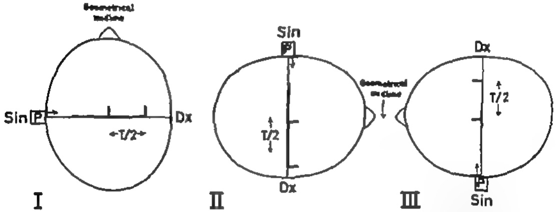

Figure 14 Schematic presentation of echoencephalograms with regard to midline echo and distal lateral ventricle echo in an infant with moderate *hydrocephalus, recorded from the left test point* (P = the probe) The figure shows displacement of the midline echo and the lateral ventricle echo in the right lateral position (II) as well as minimal displacement of the midline echo in the left lateral position (III) compared to the supine position (I).

Figure 14 shows schematically the results obtained with respect to the right lateral ventricle, on examination of an infant with moderate hydrocephalus. On examination in the supine position (I) the lateral ventricle index was calculated to be 0.60. With the right lateral position (II), fairly considerable deviation of the right lateral ventricle echo was noted, and a lateral ventricle index of 0.85 was obtained; in addition slight deviation of the midline echo to the right was observed When the infant was examined in the left lateral position (III) (with its head resting against the probe (P)) no deviation of the right lateral ventricle echo was noted, but slight deviation of the midline echo to the left was seen.

Ray 4 falls at right angles to D and the reflected ultrasound returns to the same point on P from which it is transmitted.

Since the distance P—D is greater than P—C, it takes longer time for ray 4 to return to P after reflection against D than for ray 1 after reflection against C therefore in the echogram the distance from the initial complex to $Echo_D$ must be longer than to $Echo_C$. If the distance between $Echo_C$ and $Echo_D$ is small, these echoes will con erge in the oscilloscope and will appear as double-peaked broad based echo.

It is thus evident from the above that

1) the amplitude of the echo increases with the curvature radius of a reflecting surface (e.g. a dilated lateral ventricle) and
2) a reflecting surface of irregular configuration may give echoes that are multi peaked and increased in width (e.g. small ventricles with irregularly formed surfaces).

In figure 17 an attempt is made to show how reflection against concave and convex spherical surfaces may influence the echoencephalographic recording.

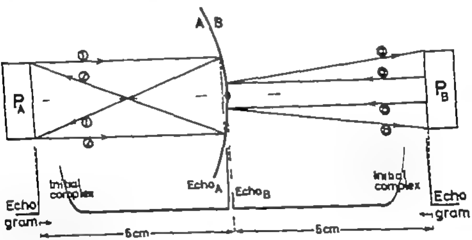

Figure 17 Amplitude of the echo in relation to conca and con ex reflecting surfaces. See tex for further details

A (Fig. 17) shows concave, spherical surface (≡ the lateral wall of the distal lateral entricle at an EVG-examination) with radius of 5 cm, reflecting parallel ultrasound; it is imagined tha the ultrasound is transmitted from probe (P_A), 2 cm in diameter placed with the centre of its radiating surface in the centre of the sphere, 5 cm from 0. All ultrasound that is transmitted from P_A and reflected against A returns to P even the marginal rays 1 and 2, because of the focusing properties of the concave surface thus an echo of high amplitude will ppear from surface A.

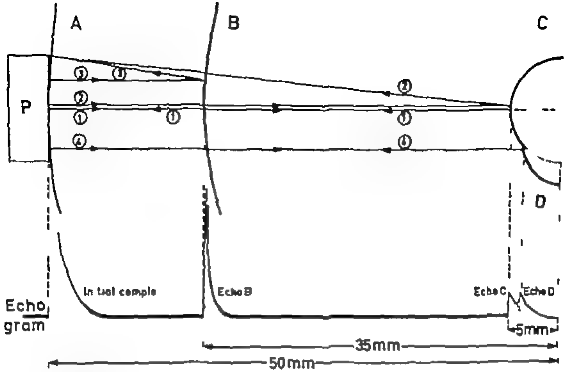

Figure 16. Amplitude of the echo as a function of the curvature radius of the reflecting surface, and demonstration of multi-peaked, wide echoes. See text for further details.

In Figure 16, it is imagined that a parallel ultrasound beam is transmitted from the probe (P), which is held closely against a spherical surface (A) with a radius of 50 mm (cf an infant's head). In its path, the beam encounters a spherical surface (B) with a radius of 35 mm (cf a dilated lateral ventricle) and also a spherical surface (C) with a radius of 5 mm the lower part of the circumference of sphere C is contiguous to a curved surface (D) with a smaller curvature radius than C (cf a small lateral ventricle or a dilated third ventricle) The central ray (1) falls at right angles to both B and C, and reflected ultrasound returns to the same point on P from which it was transmitted. Ray 2 falls against C at such an angle that the reflected ultrasound returns to the outer margin of P; thus only ultrasound that is transmitted from P from within a radius of the same order of size as the distance between rays 1 and 2 can be detected by P after reflection against C. Ray 3 falls against B at such an angle that the *reflected ultrasound* reaches the outer margin of P thus ultrasound that is transmitted from P from within a radius of the same order of size as the distance between rays 1 and 3 can be detected by P after reflection against B Since the returning intensities are proportional to the effective transmitting surface, and the amplitudes are proportional to the square root of the intensities (p. 14), it follows that the amplitudes of the echoes are proportional to the radii of the effective transmitting surfaces.

The radius between rays 1 and 3 is considerably greater than that between rays 1 and it follows that the amplitude of an echo resulting from reflection against spherical surface with a large curvature radius ($Echo_B$) must be greater than that of an echo occurring from reflection against a spherical surface with a small curvature radius ($Echo_C$).

Ray 4 falls at right angles to D and the reflected ultrasound returns to the same point on P *from which it is transmitted.*

Since the distance P—D is greater than P—C, it takes a longer time for ray 4 to return to P after reflection against D than for ray 1 after reflection against C; *therefore in the echogram* the distance from the initial complex to $Echo_D$ must be longer than to $Echo_C$. If the distance between $Echo_C$ and $Echo_D$ is small, these echoes will converge in the oscilloscope and will appear as a double-peaked broad based echo.

It is thus evident from the above that

1) the *amplitude of the echo increases with the curvature radius of a reflecting* surface (e.g. a dilated lateral ventricle) and
2) a reflecting surface of irregular configuration may give echoes that are multi-peaked and increased in width (e.g. small ventricles with *irregularly* formed surfaces).

In figure 17 an attempt is made to show how reflection against concave and convex spherical surfaces may influence the echoencephalographic recording.

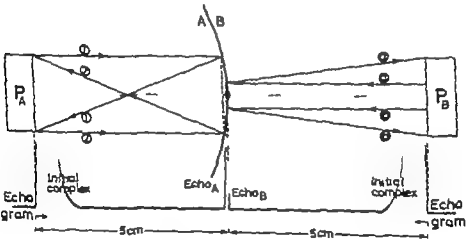

Figure 17. Amplitude of the echo in relation to concave and convex reflecting surfaces. See text for further details.

A (Fig. 17) shows a concave, spherical surface (e.g. the lateral wall of the distal lateral ventricle at an EVG-examination) with a radius of 5 cm, reflecting parallel ultrasound. It is imagined that the ultrasound is transmitted from a probe (P_A), 2 cm in *diameter placed* with the centre of its radiating surface in the centre of the sphere, 5 cm from 0. All ultrasound that is transmitted from P_A and reflected against A *returns to P* even the marginal rays 1 and 2, because of the focusing properties of the concave surface; thus an echo of high amplitude will appear from surface A.

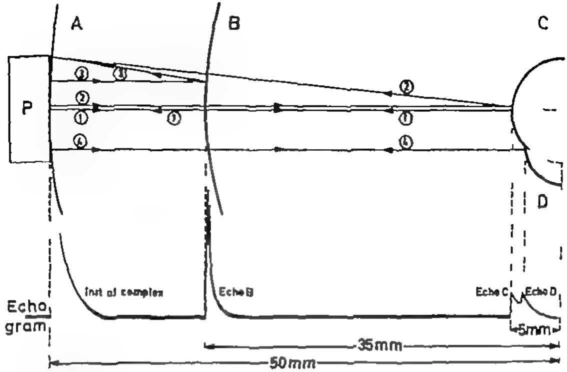

Figure 16 Amplitude of the echo as a function of the curvature radius of the reflecting surface and demonstration of multi-peaked, wide echoes. See text for further details.

In Figure 16, it is imagined that a parallel ultrasound beam is transmitted from the probe (P) which is held closely against a spherical surface (A) with a radius of 50 mm (cf an infant's head); in its path, the beam encounters a spherical surface (B) with a radius of 35 mm (cf a dilated lateral ventricle) and also a spherical surface (C) with a radius of 5 mm; the lower part of the circumference of sphere C is contiguous to a curved surface (D) with a smaller curvature radius than C (cf a small lateral ventricle or a dilated third ventricle). The *central ray (1) falls at right angles to both B and C, and reflected ultrasound returns* to the same point on P from which it was transmitted. Ray 2 falls against C at such an angle that the reflected ultrasound returns to the outer margin of P thus only ultrasound that *is transmitted from P from within a radius of the same order of size as the distance between* rays 1 and 2 can be detected by P after reflection against C. Ray 3 falls against B at such an angle that the reflected ultrasound reaches the outer margin of P; thus ultrasound that *is transmitted from P from within a radius of the same order of size as the distance between* rays 1 and 3 can be detected by P after reflection against B. Since the returning intensities are proportional to the effective transmitting surface, and the amplitudes are proportional *to the square root of the intensities (p. 14), it follows that the amplitudes of the echoes* are proportional to the radii of the effective transmitting surfaces.

The radius between rays 1 and 3 is considerably greater than that between rays 1 and 2 it follows that the *amplitude of an echo resulting from reflection against a spherical surface* with a large curvature radius (Echo$_B$) must be greater than that of an echo occurring from reflection against a spherical surface with a small curvature radius (Echo$_C$)

ointment is easy to remove, and is possibly preferable for adults and older children with thicker and coarser hair

Owing to the fineness and sparsity of an infant's hair it is not necessary to shave the part of the head where the probe is to be placed, in order to obtain good contact and to avoid totally reflecting air masses between the surface of the probe and that of the head. It is more difficult however to obtain good contact between the probe and the surface of the head in infants than in adults, especially as infants seldom lie absolutely still further due to the plane surface of the probe (cf p. 43), difficulties may be encountered in finding a sufficiently large plane surface on an infant's small, often bulging head, to obtain a large enough effective transceving area.

On echoventriculographic examination, the amplification of the apparatus must be varied so that both the midline and bottom echoes, and the ventricular and parenchymal echoes can be detected, in order that any echo-free zones can be ascribed their correct diagnostic value. An echoencephalogram representing the intracranial anatomy is reproducible artefact echoes vary however from one examination to another in the same patient. If an echoencephalogram with uncharacteristic, flat, irregularly shaped echoes is obtained, the examination should be repeated after removing the contact medium from the two surfaces and making a fresh application.

The probe must be rocked and moved slightly against the head until an ideal (or almost ideal) echo is recorded, which means that the ultrasound falls at right angles to the reflecting surface being examined otherwise, accurate calculation of distances will not be possible. Therefore, the localization of the probe on the patient's head cannot be defined mathematically as so many millimetres from, for example, the external auditory opening, owing to individual variations in the configuration of both the entire head and the lateral ventricles, it is necessary to seek a region from which as ideal echoes as possible can be found.

Midline control

For psychological reasons I have found it best in infants and children to start the examination with the midline control. This is quickly performed and gives the patient no time to become irritated. When experience has then taught him that the examination is not harmful it is usually possible to continue undisturbed with the stages that require greater concentration, namely the search for the midline and ventricle echoes. In the few cases in which the subsequent echo recording cannot be made from the same point as for the midline control, for example owing to the shape of the skull, a new midline

B (Fig. 17) is the convex surface of the same sphere, *reflecting parallel ultrasound* (e.g. the proximal wall of a lateral ventricle at an echoencephalographic examination) it is imagined that this ultrasound is transmitted from a probe (P_B) also with a diameter of 2 cm, placed outside the convex surface with its centre 5 cm from 0. Parallel ultrasound transmitted from P_B is reflected in B as divergent rays only rays that are transmitted from the centre of P_B within a diameter equal to the distance between rays a and b, return to P_B after reflection.

The diameter between rays 1 and 2 (from the concave reflecting surface A) is considerably greater than that between rays a and b (from the convex surface B) it follows (cf pp. 14 and 48) that the echoes from the concave surface will be of greater amplitude than the corresponding echoes from the convex surface.

The distance between the surface of the probe and the reflecting region is somewhat shorter for the marginal rays 1 and 2 than the corresponding distance for the marginal rays a and b from this it follows that the distance between the initial complex of the echogram and the echo from the concave surface ($Echo_A$) is not completely identical with the corresponding distance to the convex surface ($Echo_B$).

It is evident from the above that echoes from parallel ultrasound, transmitted from the same probe at the same distance from a curved reflecting surface

1) will be of higher amplitude when the reflecting surface is positioned so that it is concave, than when it is convex
2) will appear at a somewhat smaller distance from the probe when the reflecting surface is concave, than when it is convex.

V COMMENTS CONCERNING THE METHOD

Position of the head

In an EVG examination special attention must be paid to the position of the infant's head to avoid errors in the assessment due to intracranial displacements (cf p 46 and Fig. 14) It is therefore of advantage if the EVG examination is always performed in the supine position.

Application of probe

As a contact medium between the surface of the head and the probe liquid paraffin is preferable to more viscous media such as, for example, the water soluble ointment which is supplied with the apparatus. Liquid paraffin usually gives good contact and allows sliding of the probe on the surface of head for the EVG examination. With the contact ointment, each time the probe needs to be moved a new application of ointment is required on the other hand this

ointment is easy to remove, and is possibly preferable for adults and older children with thicker and coarser hair

Owing to the fineness and sparsity of an infant's hair it is not necessary to shave the part of the head where the probe is to be placed, in order to obtain good contact and to avoid totally reflecting air masses between the surface of the probe and that of the head. It is more difficult however to obtain good contact between the probe and the surface of the head in infants than in adults, especially as infants seldom lie absolutely still further due to the plane surface of the probe (cf p. 43) difficulties may be encountered in finding a sufficiently large plane surface on an infant's small, often bulging head, to obtain a large enough effective transceiving area.

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The probe must be rocked and moved slightly against the head until an ideal (or almost ideal) echo is recorded, which means that the ultrasound falls at right angles to the reflecting surface being examined otherwise, accurate calculation of distances will not be possible. Therefore, the localization of the probe on the patient's head cannot be defined mathematically as so many millimetres from, for example, the external auditory opening owing to individual variations in the configuration of both the entire head and the lateral ventricles t is necessary to seek a region from which as ideal echoes as possible can be found.

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control is made from the same area on the head at which the probe must be placed for the echo recording

Echo examination

In order to obtain ideal echoes, the distal lateral ventricle echo is more suitable than the proximal one partly for geometrical reasons because of the focusing properties of a concave reflecting surface (cf p 50) and partly because the proximal echo may lie so far laterally that it disappears in the initial complex or appears within the near field, where gross amplitude distortion may occur (cf p 43)

Echoes from a curved surface with a large radius have a higher amplitude than when the radius is small (cf p 48) Thus it is possible to obtain ideal echoes from the lateral wall of the distal lateral ventricle when the ventricular system is dilated which makes it possible to determine fairly exactly the size of dilated ventricles.

It is more difficult and sometimes impossible, to obtain ideal echoes from a normal lateral ventricle its curved and often irregularly shaped surface with a small curvature radius will give multiple mutually confluent echoes of low amplitude (see p 49) measurements of the ventricular size in normal infants and children will therefore be more approximative than in patients with a dilated ventricular system However a normal echoencephalogram in paediatric patients is characterized by parenchymal echoes covering almost the whole recording therefore it is not necessary for diagnostic purposes, to obtain an exact value of the lateral ventricle index in order to make sure that the lateral ventricles are not dilated

In patients with thicker skull bone the higher degree of absorption (cf p 17) may cause the distal ventricle echo to disappear but it may still be possible to obtain echoes from the proximal lateral ventricle. For compatible results, it is necessary to use comparable surfaces since the echoes from a concave and a convex surface of the same curvature differ somewhat (cf p 49)

On its pathway through the brain ultrasound passes through different tissues at somewhat varying speeds. However the differences in sound velocity in the brain (1515 m/sec) and cerebrospinal fluid (1504 m/sec) (cf p 14) are so small as to be negligible in an echoencephalogram a difference of less than 2/3 mm would be obtained if the skull cavity were full of cerebrospinal fluid instead of cerebral parenchyma.

A reflecting structure composed of several differently positioned components with acoustic properties differing from those of the environment may give rise to a broad based, multi peaked echo complex that is in such cases where

the different reflecting components lie so close together as to give confluence of the individual echoes on the echoencephalogram this will be seen in patients with cerebral tumour structures or in cases of dilated third ventricle where the dilatation does not reach such a degree *as to give individual echoes* from each of its lateral walls, separated by an echo-free zone.

Summing up: Broad-based, multiple-peaked echoes of low amplitude may be an expression of

1 the character of the reflecting structures, e.g. a dilated third ventricle or a tumour
2. the geometry of the structures and ultrasonic beam, e.g. in cases where the probe is not lying parallel with the reflecting *surface or the contour of the* reflecting surface is irregularly shaped
3 poor contact between the probe and the surface of the head.

By careful investigation and an aim at reproducibility of the results, it can usually be determined from the oscilloscopic tracing which of these factors is the underlying cause.

Photographic recording

The photographic recording constitutes only one, and at times a less important part of the whole examination.

When performing EVG it is not always possible to obtain a photographic recording that fully justifies the tracing observed in the oscilloscope. An ideal echo seen in the oscilloscope may be of lower amplitude, and sometimes broader on the photographic recording, for example if the patient moves his head just at the moment when the photograph is taken, so that the probe lies at a slight angle *to the echo-producing surface. It is essential, therefore,* that the photographic recording is assessed at the time of the examination, so that, if necessary the recording may be repeated so as to agree with the oscillogram.

Graphical rep esentation

*If the EVG examination has been carried out with care and with the avo*idance of the sources of error discussed above, evaluation of the photographic recording *according to the described* method of graphical representation and index calculation can, after a short period of training, be performed simply and quickly This will give a clear picture of the ventricular system in relation to the external diameter of the head when presenting a report on the result of the EVG examination I usually enclose a copy of the diagram, with the external contours of the head and ventricles *dotted in* approximately over

control is made from the same area on the head at which the probe must be placed for the echo recording

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after a shunt operation, a constant value, or a decrease of the I value, indicates a well functioning shunt- an increase of I may be the first sign of an occlusion of the shunt (unpublished observations).

General considerations

Echoventriculography is an anatomical examination, similar in this respect to cerebral pneumography. From the primary results observed in the oscilloscope, the subsequent course of the examination is decided. For optimal results of this examination it should be performed, like pneumography by a physician who is experienced in the technical matters involved, has knowledge of the anatomy of the ventricular system and the physics of sound beams and is capable of three-dimensional conception.

Only in regions of the interfaces of the ventricular system which run parallel with the surface of the skull on which the plane probe surface is placed, can detailed echoencephalographic analysis be made this is a disadvantage of the echo method with the commercial echoencephalographic equipment available, since the probes are not especially adapted for studies of the ventricular system in infants. On the other hand, where ideal echoes are registered this method is one of high accuracy which allows fairly exact measures of the size of the lateral ventricles in physiological conditions.

VI. SUMMARY

The echoencephalographic examinations in this study were performed with a commercial echoencephalograph, which was found to be linear for the measurements in question.

Definitions

A method for ultrasonic A-scan examination with special regard to evaluation of the size of the ventricles in infants and small children is presented in detail such an examination has been called *echoventriculography* and the photographic recording of the results an *echoventriculogram (EVG)* An EVG comprises a midline control recording together with an echoencephalogram from the right and one from the left temporal region the position on the head at which the probe is placed in an EVG recording has been called the *test point* Closely occurring echoes of low amplitude which are recorded from the cerebral parenchyma have been designated *parenchymal echoes*

it. The index calculation gives a practical and precise expression of the size of the ventricles in relation to the actual diameter of the head, which is of especial value in paediatric practice with growing patients.

In addition this method of graphical representation gives an extra check with regard to the identification of the recorded echoes in cases where, for example both proximal and distal lateral ventricle echoes are obtained on the echoencephalograms from both the right and the left side, the proximal lateral ventricle echo from the right echoencephalogram will be on essentially the same vertical line in the diagram as the distal lateral ventricle echo from the echoencephalogram made from the left side.

Lateral ventricle index (I)

The index calculation means independence of the setting and calibration of the apparatus at the examination and permits direct comparison with, for example, cerebral pneumography without conversion of the width of the ventricles into ordinary units of measurement.

Furthermore, this method eliminates the sources of errors which a wide midline echo or variations in the breadths of the superficial structures, will produce when measuring the width of a lateral ventricle from the midline echo to the lateral ventricle echo or the parenchymal thickness from this echo to the bottom echo

The lateral ventricle index (I) is of especial value for follow up examinations of hydrocephalic infants.

For example, if an infant with hydrocephalus is examined on two different occasions, the lateral ventricles, in absolute measurements, may certainly show an enlargement, but on the other hand in relation to the cranial diameter on the second occasion they may be found to be relatively smaller than at the first examination so that in actual fact the hydrocephalic expansive process will have regressed

when one and the same value is obtained for I in an infant with a growing head at different times of examination it is clear that the hydrocephalic process is not progressing at the cost of the cerebral parenchyma—thus that the ventricles are growing only proportional to the cranial circumference—and there is usually no urgency for performing a shunt operation

on the contrary an increase of the value for I indicates an active hydrocephalic process with expansion of the ventricles at the cost of cerebral parenchyma this can be diagnosed—and a shunt operation performed—before any noteworthy increase in head circumference has been observed

In the examination liquid paraffin was used as contact medium between the probe and the surface of the head, thus allowing smooth movement of the probe along this surface. The layer of contact medium must be thin enough to be regarded as negligible when measuring the distances.

The patients were examined in the symmetrical horizontal position in echoencephalographic examinations of hydrocephalic patients, lateral deviation of both the lateral ventricle echo and the midline echo can be noted when the lateral position is used, compared with the supine position.

An echoencephalogram corresponding to the intracranial anatomical conditions can always be reproduced.

Using the above method, determination of the relative size of the lateral ventricles in infants with hydrocephalus can be performed with a standard deviation of 2 %, while for geometrical reasons associated with the beam, evaluation of the size of lateral ventricles of normal width is more approximate.

Completely *echo-free zones* which have remained echo-free even at maximal amplification of the apparatus, have been found, on comparison with the pneumogram to correspond to fluid filled intracranial spaces.

The name *lateral ventricle echo* has been given to the echo which laterally delimits an echo-free zone which in turn is medially divided by the midline echo

On reflection of ultrasound against a plane surface lying parallel to a plane probe surface, echoes of high amplitude are obtained, which rise practically at right angles to the time axis of the oscilloscopic tracing. Such echoes have been called *ideal echoes* only ideal echoes allow accurate distance evaluations Multiple, mutually confluent echoes of low amplitude are referred to collectively as *wide echoes* wide echoes may be due either to the properties of the reflecting structures or the geometry between the structures and the ultrasonic beam. Wide echoes *arising from faults or deficiencies in the technical procedure* of the examination have been called *artefact echoes*

Method

An echoencephalographic examination with special regard to the ventricular system consisted of the following stages

1) an orientational examination at which the oscilloscopic tracing was studied with regard to the overall impression individual echoes and echo-free zones, while the position of the probe was carefully varied over the respective test points, and while the amplification of the apparatus was also varied
2) recording of EVG when the tracing in the oscilloscope was reproducible in all respects
3) "scanning" over the patient's head (with the A scan equipment) while the oscilloscopic tracing was being studied, and also photographic recording of any noteworthy echoencephalograms from sites other than the test point, including a midline control from the same site,
4) preliminary interpretation of the EVG and any other recordings made at the examination and also any necessary complementary examinations in cases where the recordings were not representative of the overall picture in the oscilloscope,
5) measurement of the EVG and any paratemporal recordings graphical representation and calculation of indices,
6) summarizing evaluation with regard to the appearance of the ventricular system and any pathological conditions.

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GENERAL DISCUSSION

Physical calculations show how the potentialities of different ultrasonic frequencies for recording echoes from the interface between cerebrospinal fluid and brain parenchyma are influenced by the skull thickness (Fig. 2) they show further that on echoencephalography the orders of magnitude of the thermal, mechanical and molecular effects of the ultrasound are such that sufficiently broad margins exist before any injurious effects can occur and thus the method can be regarded as entirely harmless even for examinations of newborn babies.

With the ultrasonic echo method, exact determinations of distances are only possible under the condition that ideal echoes—which rise practically at right angles to the time axis of the oscilloscope—are obtained.

For physical reasons, ideal echoes are sometimes impossible to record from the intracranial structures of small infants, where echoes from, for example, the lateral wall of the lateral ventricle and sometimes also from the inner curved surface of the skull of the opposite side are not seldom combined with several small echoes arising from reflection against small surfaces at different distances from the probe.

Experimental investigations have shown, further that difficulties may be encountered in recording ideal echoes even on ultrasound reflection against a completely flat surface, if the probe is held against a curved surface with a small curvature radius, this means in clinical practice, for example, that technically it may be difficult to obtain ideal midline echoes in small infants even from a normal third ventricle situated at the midline. Consequently in infants it may be difficult and often impossible to record ideal echoes from any known intracranial structure which can constitute an exact reference point from which distances can be measured to echoes from other intracranial structures.

Therefore, in infants in whom ideal echoes have not been obtained, an echoencephalographic method which involves measurement between echoes from different intracranial structures—e.g. measurement of the width of the lateral ventricle as the distance between midline echo and lateral ventricle echo, or of the thickness of the cerebral parenchyma as the distance between lateral ventricle echo and bottom echo—will never give a reliable distance evaluation.

The echoencephalographic method presented in this study differs in principle

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GENERAL SUMMARY

Physical calculations indicate that the interface between cerebrospinal fluid and brain parenchyma can be recorded by echoencephalography under the condition that the thickness of the skull is 3 mm or less; they also indicate that the energy transferred during an echoencephalographic examination is considerably below the level at which harmful effects may occur, even in small infants.

An echoencephalographic method is presented, which was developed with especial regard to measurement of the ventricular size in infants and children, in whom, as a rule, multiple ideal intracranial echoes are not easily recordable; the measurements from the echoencephalograms are expressed, as indices, in relation to the diameter of the head, determinable precisely by an ultrasonic method, by means of a diagrammatic procedure which is simple to perform and not time consuming.

Methodological difficulties and sources of error apparent from experimental and clinical trials and physical calculations, and the way in which they could be eliminated, are discussed, as well as the advantages of expressing the ventricular size as an index in paediatric patients.

from the conventional procedure for evaluation of the echoencephalograms obtained, in that as a reference point in distance measurements the ultrasonically determined external diameter of the patient's head, which can be obtained exactly is used.

The measurement values obtained from the echoencephalograms are then expressed in relation to this diameter as indices (Fig 8) by means of a practical simple diagram procedure which takes little time. This means, firstly that conversion of the echoencephalographic measurement results to ordinary units of measurement, with possible enlargement of errors, is avoided, and secondly direct comparison of the results with those of other methods of examination, e.g cerebral pneumography becomes possible in infants with growing heads it is an advantage that the ventricular size is expressed in relation to the child's own cranial diameter

The lateral ventricle index (I) is of especial value for follow up examinations of hydrocephalic infants, where an increase of the I value will indicate an expansion of the ventricles at the cost of the cerebral parenchyma, and a decrease of the I value indicates a regression of the ventricular size (for example after an operation with a well functioning shunt) thus, the clinician can follow the actual hydrocephalic process quite independently of different cranial circumferences on different examination occasions.

Since the reference points—the outer demarcation points of the ultrasonically determined diameter of the head—are exact, then measurement to an ideal intracranial echo can also mean that this echoencephalographic method can be exact, e.g on evaluation of the size of the lateral ventricles in hydrocephalic children where the lateral walls of the lateral ventricles usually run parallel with the surface of the head and give rise to ideal echoes.

The definition of lateral ventricle echo in this study is that echo which laterally delimits an echo-free zone (from the intraventricular cerebrospinal fluid) which is divided medially by the midline echo For several reasons it has been found most suitable in determining the size of the lateral ventricles to make measurements to the distal lateral ventricle echo

In infants and children irregular echoes of low amplitude are recorded from the cerebral parenchyma an echo-free zone which remains echo-free even on maximal amplification of the apparatus thus implies a fluid filled space.

One further advantage in using the ultrasonically determined external diameter of the patient's head as reference is that echoencephalographic examinations can be made even in directions from which there are no definitely identifiable intracranial echoes of known location e.g along the longitudinal diameter of the head recordings of for example, echo-free zones in different projections of the head can therefore be evaluated and combined—in the same way as several photographs in a cerebral pneumography—to form a three-dimensional picture of the fluid filled spaces inside an infant's head.

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PROCEEDINGS O[illegible]
FIFTEENTH NORTHERN
PEDIATRIC CONGRESS

BERGEN, JUNE 28—JULY 1, 1967

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SCIENTIFIC EXHIBITIONS

Presidential Address

ALFRED SUNDAL
Department of Pediatrics, University of Bergen

Ladies and Gentlemen

On behalf of the Congress Committee and of Norwegian pediatricians I take great pleasure in welcoming pediatricians from the five Northern countries to the XVth Northern Pediatric Congress.

I also welcome our guests of honour their presence at the opening of the Congress will lend lustre to our meeting to-day and to the work we are to do together in the course of the next few days.

The Northern Pediatric Association, an amalgamation of the national associations of pediatricians in the Nortern countries, has to-day nine honorary members. In giving them this special membership it has been our desire to honour the great contribution they have made to pediatrics as a whole and, in particular to the development of pediatrics in the North Unfortunately only one of these honorary members, Professor Arvid Wallgren, of Stockholm, is present to-day We have all the more reason to thank him for coming, and to pay tribute to him as a great representative of the pediatricians of the North. The other eight honorary members, who were unfortunately not able to attend the Congress, are the following

From Denmark
Dr med. Paul Drucker
Dr med. Carl Friderichsen,
from Finland
Professor Arvo Ylppö,
Professor Viljo Rantasalo,
from Sweden
Professor Curt Gyllenswärd
Professor Nils Malmberg,
and from Norway
Dr med Arthur Collett,
Dr med. Lauritz Stoltenberg

Professor Ylppö and Dr med. Friderichsen have sent us their greetings by telegram.

We have received financial help from various industrial circles, partly through commercial displays in the building here, and I should like to express our thanks for this assistance.

Since our last meeting, in Stockholm in 1964 we have heard with regret of the death of several of our members from the national associations of pediatricians.

Professor Toivo *Salmi* of Finland died on Whitsunday 1965 at the age of 63 A native of Viborg, Karelia, Professor Salmi studied under Arvo Ylppö. In 1937 he began lecturing in pediatrics at Helsinki University and in 1945 was appointed to the newly established chair of pediatrics at Åbo University He took an active part in research work, particularly into the problems of newly born and premature infants. Social pediatrics also had a great claim on his interest.

Arvo *Arvola* died in April, 1965, at

the age of 61 He was Chief Physician of the Children's Unit of the Kotka Municipal Hospital and for the last three years of his life was Deputy Superintendent of the Central Hospital in Tammerfors.

Vuokko *Lahtiperä* died in 1965 at the age of 56 He was Chief Physician of the Isolation Hospital in Tammerfors and Municipal Medical Officer of Åbo

The following deaths have occurred among our Swedish colleagues

Professor Sture *Siwe* of the University of Lund died in April 1966 at the age of 69 He began his study of pediatrics at the Children's Hospital in Lund under his predecessor Professor af Klercker In 1936 Sture Siwe was appointed Professor of Pediatrics at the University of Lund He had wide interests in the field but is best known for his work on child tuberculosis, rickets infantile tetanus, and mental health work for children Outside Scandinavia his name is best known in connection with reticulo-endotheliosis in children the Letterer Siwe's disease

Lars Nilsson Assistant Physician of the Gothenburg Children's Hospital died in 1966 at the age of 39 The year before his death he defended his thesis for the doctorate entitled Thyroid Enlargement in Adolescence

Professor Edgar *Mannheimer* lost his life in a traffic accident in Africa in April 1965 He had been a lecturer in pediatrics at the Karolinska Institute and has led the first cardiological unit for children in the North at Kronprinsessan Lovisas Children's Hospital in Stockholm During the years preceding his death he was Chief Physician and Professor at the Swedish Ethiopian Children's Hospital in Addis Ababa He was a warm hearted enthusiastic and generous person who will be deeply missed

Sven *Huldt* Chief Physician of the Isolation Hospital in Danderyd died in October 1965

Sarah *Gyllencreutz*, practising pediatrician and school doctor in Stockholm died in March of this year

The Norwegian pediatrician Johanna *Schram Anderssen* died in October 1966 at the age of 69 She had her private practice here in Bergen her native city where the work she carried out might serve as a model for that of a practising pediatrician and family doctor

I ask the audience to stand and to pay homage in silence to the memory of our dear colleagues The contributions they made in different fields of pediatrics were of great value to the children of Scandinavia, and to the credit of the pediatric profession

We have looked forward to to-day with a certain amount of anxiety We asked ourselves several questions Would our colleagues from the other countries of the North come to Bergen? Would there be many participants or few? Should we be able to make satisfactory arrangements for such a large congress? We have been pleasantly surprised by the large number of participants — we are about 500 all told — and you are the ones to be thanked for that The question

of whether we shall be able to do our part satisfactorily must be left open for the time being

The interest we all have in common is pediatrics. Pediatrics embraces the study of the healthy and the sick child, and has as its goal the improvement of child health and the prevention and cure of disease. Our Northern congresses have the following tasks and aims the communication of the results of research, the discussion of problems with colleagues working in similar fields, the exchange of information, and mutual inspiration. Our long-term objective is that of increasing our insight and knowledge so that we shall be better able to improve health, to prevent and cure disease, to help the children of the North and the children of the world.

Medical science rolls on and research is the salient word. Considerable work is needed if progress is to be made. It would not be worthy of a country that calls itself civilized to rest on its laurels, leaving the task of further development to other nations. We must take part, as far as our abilities and circumstances allow in the gigantic work which is to a particular degree our responsibility the health of our children and the health of the nation We must endeavour to lay stone upon stone in building the edifice of pediatrics.

We live in a quiet corner of the world where we enjoy a high standard of living, social security and the services of well trained medical personell and well equipped hospitals. It must be admitted that our children have an advantage compared with many others. But this is an advantage which bears with it an obligation We must all devote ourselves to the tasks which lie waiting for specialists in pediatrics research problems, practical work as pediatricians here in Scandinavia or in the developing countries. There are many possibilities open to us if we have our eyes open and the courage to take hold.

Pediatrics is expanding It is first and foremost during childhood, when the organism is in the growth and development period, that we can influence the individual in a favourable or unfavourable direction Here in the North preventive health work with children has borne rich fruits. Curative pediatrics has expanded considerably and is continuing to develop Our insight into the pathology of childhood has never been greater than to-day

But let us not congratulate ourselves too heartily To-day we can rejoice to see more and more conquests being made in medical and pediatric sectors, but these are only possible because those who have gone before have laid a firm foundation on which we could build We must not forget that there are many steps on the ladder of pediatrics that we have yet to climb

The scientific programme of this Congress deals with topical questions. The main themes to be considered are 1) Malabsorptive disorders in pediatrics, and 2) Growth disturbances. A round table conference will throw light on the important practical question of non-obstructive urinary tract infections in children. A

the age of 61 He was Chief Physician of the Children's Unit of the Kotka Municipal Hospital and for the last three years of his life was Deputy Superintendent of the Central Hospital in Tammerfors.

Vuokko *Lahtiperä* died in 1965 at the age of 56 He was Chief Physician of the Isolation Hospital in Tammerfors, and Municipal Medical Officer of Åbo

The following deaths have occurred among our Swedish colleagues.

Professor Sture *Siwe* of the University of Lund died in April 1966 at the age of 69 He began his study of pediatrics at the Children's Hospital in Lund under his predecessor Professor af Klercker In 1936 Sture Siwe was appointed Professor of Pediatrics at the University of Lund He had wide interests in the field but is best known for his work on child tuberculosis rickets infantile tetanus, and mental health work for children Outside Scandinavia his name is best known in connection with reticulo-endotheliosis in children the Letterer Siwe's disease

Lars Nilsson Assistant Physician of the Gothenburg Children's Hospital died in 1966 at the age of 39 The year before his death he defended his thesis for the doctorate entitled Thyroid Enlargement in Adolescence

Professor Edgar *Mannheimer* lost his life in a traffic accident in Africa in April 1965 He had been a lecturer in pediatrics at the Karolinska Institute and has led the first cardiological unit for children in the North at Kronprinsessan Lovisas Children's Hospital in Stockholm During the years preceding his death he was Chief Physician and Professor at the Swedish Ethopian Children's Hospital in Addis Ababa. He was a warm hearted enthusiastic and generous person who will be deeply missed

Sven *Huldt* Chief Physician of the Isolation Hospital in Danderyd died in October 1965

Sarah *Gyllencreutz*, practising pediatrician and school doctor in Stockholm died in March of this year

The Norwegian pediatrician Johanna *Schram Anderssen* died in October 1966 at the age of 69 She had her private practice here in Bergen her native city where the work she carried out might serve as a model for that of a practising pediatrician and family doctor

I ask the audience to stand and to pay homage in silence to the memory of our dear colleagues. The contributions they made in different fields of pediatrics were of great value to the children of Scandinavia and to the credit of the pediatric profession

We have looked forward to to-day with a certain amount of anxiety We asked ourselves several questions Would our colleagues from the other countries of the North come to Bergen? Would there be many participants or few? Should we be able to make satisfactory arrangements for such a large congress? We have been pleasantly surprised by the large number of participants — we are about 500 all told — and you are the ones to be thanked for that The question

PAPERS

number of lectures are to be held on subjects other than the main themes already mentioned a total of 60 publications will be read in the course of these three days In addition there will be 28 scientific exhibitions, and these will also be of great value The scientific part of the programme will, taken all in all give a cross-section of to-day s pediatrics, and will throw light on new advances and current research.

I thank all the lecturers and exhibitors who are going to pass the results of their research on to us and inspire us to become better pediatricians.

In addition to the chairman for the main themes and the leader of the round table conference the executive council of the Northern Pediatric Association will suggest the following vice presidents

Professor Bo Vahlquist, Sweden.

Professor Ole Wasz Höckert, Finland

Chief Physician Jorgen Flamand Christensen Denmark

I trust and hope that the delegates to this Congress will gain professional enrichment and that meeting their colleagues here will prove inspiring, and will lead to the making of new contacts and new friends. With these words I hereby open the XVth Northern Pediatric Congress.

SESSION I

SUBJECT Malabsorptive Disorders in Pediatrics

CHAIRMAN Professor Bertil Lindquist

1 Physiology of Carbohydrate Digestion and Absorption

A. DAHLQVIST

Research Department of the Hospital and Department of Physiological Chemistry University of Lund

The carbohydrates in the food are mainly present as polysaccharides and disaccharides, which are hydrolyzed to monosaccharides by the enzymes in the digestive tract. The first step in the hydrolysis of polysaccharides, such as starch and glycogen, is rapidly effected by the α-amylase, secreted from the salivary and pancreatic glands. The di- and oligosaccharides formed, as well as the disaccharides present as such in the diet (e.g sucrose and lactose) are then split by the disaccharidases of the small intestine. These enzymes are not secreted, but act in the absorbing mucosal cells. The disaccharidases are localized in the superficial part of the mucosal cells, most probably in the "brush border" which has been shown both by histochemical staining methods and by in vitro incubation techniques. It is, however still a matter of dispute whether they are located on the surface of the cells, in direct contact with the lumen of the intestine, or inside a superficial cell membrane. A recent electron-microscopic study has indicated that the intestinal disaccharidases are present in small "knobs" located on the surface of the microvilli, but it remains to be demonstrated whether these structures consist of naked enzymes attached to the outside of the cell membrane or of folds of the membrane forming a kind of "ultra microvilli"

The specificity of the small-intestinal disaccharidases has been studied by several methods. Heat inactivation studies reveal that the maltase activity in the human small intestine is exerted by at least four different enzymes, maltase Ia, maltase Ib, maltase II and maltase III. The isomaltase activity appears to be caused by the same enzyme as *maltase Ia*, the sucrase by maltase Ib. In addition

2 Gastrointestinal Allergy

L. A. HANSON

Dept. of Pediatrics and Institute of Medical Microbiology
Dept. of Bacteriology University of Göteborg

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The difficulty of reaching a conclusive diagnosis in these cases was early noticed The importance of a detailed history was stressed but a search was made to find further support for the diagnosis. During the years 1906–1908 the eosinofilia of allergic disorders was demonstrated locally in the intestine as well as in the stool. Already in 1912 Schloss succeeded in relating the gastrointestinal symptoms in a case of egg allergy to a positive skin test with a protein fractionated from ovomucoid He was also able to desensitize the patient with this protein

The usefulness of the skin test in the diagnosis of gastrointestinal allergy was a matter of debate during the following years. The relation between a positive skin test to a food constituent and a gastrointestinal hypersensitivity to the food is poor with various authors reporting a correlation between 20 to 70% usually around 50% This illustrates the limited value of the skin test in the diagnosis of gastrointestinal allergy

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It would be provocative to state that this brief historical survey of gastrointestinal allergy also represents, to a considerable degree, the status of this field today A quotation from an American allergologist as late as 1948 All functional gastrointestinal disorders have an allergic cause" indicates, however that there would be some truth in such a statement. That the diagnostic difficulties still exist is made obvious by the editorial remark on a recent paper in New England Journal of Medicine noting that the diagnosis of gastrointestinal allergy in the cases studied in the criticized paper was only based on "soft deduction

In the etiology of human gastrointestinal allergy the delayed type of hypersensitivity has not yet been shown to play a role, whereas the immediate type of hypersensitivity most probably is an important mechanism.

there is, however, one trehalase and one lactase. Chromatographic studies have supported these results but sucrase and lactase are further subfractionated into two components each on Sephadex columns The two sucrase fractions have very similar properties and it is uncertain whether the two fractions really represent different enzymes. The two lactase fractions in contrast, show marked differences in their enzymatic properties. They also differ in localisation One of them seems to be located in the brush border of the mucosal epithelial cells, like the other disaccharidases while the other one is soluble in the cell cytoplasm, or possibly lysozomal In lactase deficiency only the first one is absent.

After completed hydrolysis of the ingested polysaccharides and disaccharides the carbohydrates are transported through the mucosa in the form of monosaccharides. Glucose and galactose are transported via a specific mechanism which has the characteristic that these two monosaccharides can be transported against a concentration gradient. For a long time it was believed that the glucose galactose transport involved a phosphorylation-dephosphorylation reaction but this theory has now been abandoned On the basis of newer research it has been concluded that glucose and galactose are transported into the mucosal cells via a membrane bound carrier which can only bind the sugars if it can simultaneously bind sodium ions. The carrier does not itself influence the flow direction but only facilitates diffusion across the membrane. The accumulation of the sugar is effected by the simultaneous action of an energy linked sodium pump present in all cells, which transports sodium out of the cell and thus maintains the low intracellular sodium concentration Although the carrier has not yet been isolated and characterized a large number of experiments support the validity of this theory for the active transport of glucose and galactose

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2. Gastrointestinal Allergy

L. A. HANSON

Dept. of Pediatrics and Institute of Medical Microbiology
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3 Laboratory Diagnosis of Malabsorption

G. MEEUWISSE

Department of Pediatrics, University of Lund

Steatorrhea, an important though not invariable symptom in intestinal malabsorption and pancreatic insufficiency is present when on an average diet the total fat excretion (6) exceeds 5 g (from puberty and onwards 6 g) During infancy a maximum of 10 per cent of dietary fat should be excreted Turbidimetric measurement of lipemia after a cream meal is a useful method for quick estimation of fat absorption (3 4) Pancreatic insufficiency can be screened by measuring chymotrypsin activity in a random feces sample (5) Detection of cystic fibrosis by measuring sweat electrolytes (2, 7) is important. The normal concentration of Na^+ and Cl^- is below 60 mEq/L.

Deficient xylose absorption speaks in favor of malabsorption (e.g celiac disease) After 15 g D-xylose/ sq m. orally as a 10 per cent solution the blood xylose concentration should normally exceed 15 mg per cent after 30 min. and 25 mg per cent after 60 min., these being better criteria than the urinary xylose excretion.

In the author's material of confirmed cases of diseased small intestine (by jejunal histology) among other cases of suspected malabsorption, the xylose absorption test and the serum turbidity after a cream meal (1 g fat/kg) were usually both pathological, but sometimes only one of them. Steatorrhea was usually but not always present. Other investigators (8) also found a combination of different absorption tests (xylose, FIGLU fat excretion) to be more diagnostic than any single test.

Sugar malabsorption will be suspected when watery diarrhoea with a pH of the stool below 5 is present. Fecal lactic acid excretion will then probably be increased (normally around 100 mg/24 h. in breast-fed infants and below 2.. mg/24 h. in other children) Many infants with sugar malabsorption also have increased fecal sugar (above 0.25 per cent of wet weight) A simple ward test by Clinitest[R] has been proposed (1) However this method — like other reduction methods — does not reveal fecal sucrose in sucrose malabsorption. Oral sugar loads of 30–50 g/sq.m. or 2 g/kg should normally increase the blood sugar level by at least 20 mg per cent. Fructose loads may normally give a flat blood sugar curve.

Routine clinical tests for quantitative protein absorption are not available. In the malabsorption syndrome a low serum albumin may be due to malabsorption, but also to protein loss through the intestinal wall. This can be tested by several isotope methods (^{131}I albumin ^{131}I PVP ^{51}Cr albumin and ^{59}Fe-Imferon)

Hematological studies and other methods to reveal deficiency of iron, vit. B_{12} or folic acid may give addi-

In the latter type of allergic mechanism the allergen induces in certain most probably genetically disposed individuals the formation of reagins These cell fixed antibodies release the chemical mediators of the allergic symptoms on their reaction with the homologous allergen.

The constituents of our food get into close contact with immunocompetent cells in the gastrointestinal tract. This is well illustrated by the finding of Lippard et al from 1936 that up to 80% of infants still had antigenic milk proteins demonstrable in their blood after cow s milk feeding The appearance of these circulating antigens was soon followed by precipitating antibodies in a high frequency Using the immunofluorescence technique Heremans and his associates have recently shown the formation of antibodies to food proteins in plasma cells in local intestinal lymph glands from non allergic individuals This indicates a local gastrointestinal antibody response. According to recent experimentation this local antibody response is made up of γA globulins of a special secretory type. The importance of this is still under investigation From animal experiments by Farr and his associates it is obvious however that an antigen (bovine serum albumin) induces as strong an antibody response given orally as if given subcutaneously in oil or intravenously

Many types of antibodies to foods often in high frequency have been reported by several authors using methods such as precipitation and agglutination which detect regular antibodies and not reagins. Such antibodies have no etiological relationship to any hypersensitivity and are thus very useful in diagnostic work It is possible however that they may sometimes represent blocking antibodies instead which can give protection against the allergen reagin reaction

Simple and reliable methods to demonstrate the etiologically important reaginic antibodies should be diagnostically very helpful but such methods are not yet available. The skin test is based on the activity of skin fixed reagins but obviously the presence of such reagins is a poor indicator of the presence of symptom releasing reagins fixed to cells in the shock organ the gastrointestinal tract. The Prausnitz Küstner test, which demonstrates circulating reagins, also shows a rather poor relation to gastrointestinal allergy (Heiner et al.) Encouraging results have been reported however from direct provocation of the shock-organ by testing in the rectal mucosa or by giving the suspected allergen in contrast liquid followed by studies of the gastrointestinal changes by X ray

The clinical diagnosis of gastrointestinal allergy must still mainly rest on a detailed history followed by elimination and provocation tests which are time consuming and sometimes dangerous.

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4 Histopathology of the Small Bowel in Malabsorption States

P KUITUNEN

Children's Hospital, University of Helsinki

Since 1962 small intestinal biopsies have been performed at the Children's Hospital University of Helsinki. The Brandborg Rubin multipurpose tube has been used in 56 biopsies, of which 46 were performed on children under 2 years and the Crosby Kugler capsule in 146 biopsies of which 100 were performed on children under 2 years Two perforations occurred, the one in a 10-year-old girl with the Brandborg Rubin multipurpose tube and the other in a 5-months-old boy with the Crosby Kugler capsule (port size 2.5 mm)

In studying the duodeno-jejunal mucosa the following criterions for the villous height were used a normal mucosa over 300μ, slight mucosal changes 250–300μ partial villous atrophy (PVA) 150–250μ, and subtotal villous atrophy (SVA) under 150μ. Atrophy of the small intestinal mucosa was as a rule associated with other changes such as flattening of villous epithelial cells, vacuolization

and "round" cell *infiltration* in the villous epithelium. The brush border and the basement *membrane* were indistinct. The crypts of Lieberkühn were very *often elongated*. In the lamina propria there was a lymphocytic, and sometimes *also a plasma cell* infiltration.

The *histopathological changes* in the duodeno-jejunal mucosa showed a good *correlation* with the *results* of absorption tests (the D-xylose excretion and the *faecal fat excretion*)

If the patients had been on an elimination diet *(cow's* milk free and/or gluten free diet) for a long time the correlation was less significant.

A normal small intestinal mucosa was found in patients without absorption defects and in secondary malabsorption syndrome (pancreatic insufficiency disaccharide malabsorption and after resection of a large portion of the small intestine)

Slight mucosal changes were seen in patients who had chronic or recurrent diarrhoea with transient absorption defects, and in patients who had chronic malabsorption syndromes of unknown aetiology

A partial or subtotal villous atrophy seems to indicate a primary malabsorption syndrome with gluten intolerance. Some of these patients were also intolerant to cow's milk. Intolerance of cow's milk only occurred *in isolated cases*.

The histopathological findings are summarized in table 1 Subtotal villous atrophy is patognomonic for *the primary* malabsorption syndrome (39 patients out of 41) and a partial *villous atrophy* almost patognomonic (8 patients out of 11) Slight mucosal changes are unspecific and seldom indicate the primary malabsorption syndrome. A normal duodeno-jejunal mucosa excludes the possibility of the primary malabsorption syndrome.

Specific treatment had a favourable effect on the histology of the small intestinal mucosa, but a normalization was seen only in very few cases during a follow-up time of 1/2—2½ years.

Specific changes in the small intestinal mucosa such as in Whipple's disease, intestinal lymphangiectasy and acanthocytosis were not seen in our series.

TABLE. Summary of Histopathological Findings in Various Clinical Groups.

	Duodenojejunal histology			
	Normal mucosa	Slight changes	Partial villous atrophy (PVA)	Subtotal villous atrophy (SVA)
Number of patients	28	13	11	41
Primary malabsorption syndrome	0	3	8	39
"Others"	9	9	3	2
Patients without absorption defects	17	1	0	0

Sec. malabsorption syndrome

Chronic malabsorption syndrome of unknown aetiology

Transient absorption defects

5 Malabsorption of Sugars

B. LINDQUIST

Department of Pediatrics, University of Lund

10 years ago Durand (Italy) described an infant with chronic diarrhoea which was probably due to an insufficient splitting of lactose A short time thereafter Holzel (England) and Weijers (Holland) reported cases of diarrhoea in infancy caused by deficiency of lactase and invertase respectively

Clinical forms Two types of sugar malabsorption are seen (1) Conditions due to deficiency of one or more intestinal disaccharidases (2) Conditions due to disturbance in the transport of monosaccharides across the intestinal mucosa. Of both types there exist primary (congenital) as well as secondary (acquired) forms (see table 1)

Clinical picture Disaccharide and monosaccharide malabsorption show the same clinical picture The reason for this is that the diet contains practically no free monosaccharides and furthermore that the disaccharides must be split into monosaccharides before they can be absorbed The main symptom is diarrhoea of osmotic and/or fermentative type. In the congenital forms the stools have a watery consistency and resemble urine The onset of symptoms depends on when the intolerant sugar is introduced in the diet e g in lactase deficiency symptoms start soon after the first feeding It should be noted that in the beginning the general condition is good, the children eat with good appetite Dehydration may thus be prevented for a long time. Sometimes a slight steatorrhoea is seen due to a shortening of the intestinal passage time. When the children grow older the symptoms have a tendency to subside. In the secondary (acquired) forms the diarrhoea is more moderate. Sometimes the disorder shows a subclinical picture diarrhoea is of minor importance and the only symptoms might be colic, meteorism and flatulence when the patient consumes too much carbohydrates.

Etiology The congenital forms are all probably hereditary disorders inherited in an autosomal recessive way Several cases in the same family are often seen e g in glucose galactose malabsorption In invertase-isomaltase deficiency a reduced enzyme activity has been demonstrated in the parents of the patients.

The acquired forms are probably secondary to unspecific lesions of the intestinal mucosa Secondary lactase deficiency may thus be sequelae to intestinal infections. The frequency of individuals with more or less marked lactase deficiency may in certain groups be as high as 10% or more.

The question has therefore been discussed of whether certain human beings, like many other species, lose their capacity of producing lactase

later on in life If the milk consumption is low there will not be any history of milk intolerance.

Diagnosis Sugar malabsorption is diagnosed in the following ways (1) Estimation of fecal sugar This may be used as a screening test in infancy Normally no sugar can be demonstrated in faeces. (2) Oral sugar loading tests with different mono- and disaccharides. Loading with the intolerant sugar will result in a flat blood curve. (3) Measurement of disaccharidase activity in biopsy specimens of the intestinal mucosa. (It should be noted that the histology is normal in the primary forms of sugar malabsorption.) (4) Intubation studies of intestinal absorption. This technique which permits a simultaneous measurement of the absorption rate of different sugars, is especially used for confirming the dignosis of glucose-galactose malabsorption.

TABLE I Clinical Forms of Sugar Malabsorption.

	Monosaccharide malabsorption	Disaccharide malabsorption
Primary (congenital) Forms	Glucose-galactose malabsorption	(Immaturity of lactase producing mechanism) Lack of lactase ("Alactasia") Severe lactose intolerance(?) Combined lack of invertase and isomaltase Combined lack of invertase, isomaltase and maltase(?)
Secondary (acquired) Forms	Monosaccharide malabsorption in young infants of unknown etiology Monosaccharide malabsorption in Celiac disease Mucoviscidosis Enteritis Malnutrition	Acquired lactase deficiency of unknow etiology Disaccharide deficiency in Celiac disease (Sprue) Mucoviscidosis Enteritis Kwashiorkor Malnutrition

5 Malabsorption of Sugars

B. LINDQUIST

Department of Pediatrics, University of Lund

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the age of 7–10 months. The duration of intolerance to gluten is independent of the age. On the average clinically active intolerance lasts 6–12 months, but apparently latent intolerance may remain for life.

The theories which relate to the ethiopathogenesis of malabsorption syndrome with intolerances (celiac disease) are discussed. A hypothesis is presented that there is a primary process, which damages the intestinal mucosa, so that the toxic effect of the gluten-born peptides can act and destroy the structure of mucosa. Subsequently an immunological process against gluten also comes into being. The primary process may be cow's milk allergy, infection, or congenital defect, etc.

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7 Dipeptidase Activity in Small Intestinal Mucosa in Patients with Gluten-Induced Enteropathy

T LINDBERG

Department of Physiological Chemistry and Department of Pediatrics, University of Lund

The intestinal dipeptidases constitute a group of enzymes in the intestinal mucosa which take part in the final digestion of the protein (for ref. see 1). The significance of the intestinal dipeptidases in various pathological conditions of the gastrointestinal tract is unknown. By a spektro-photometric assay method (2) the activities of nine different dipeptides in small intestinal biopsy specimens from about 120 patients (adults and children) with various gastrointestinal disorders have now been investigated.

The material includes three adults and four children with gluten-induced enteropathy. The results from the adults have been reported previously (3). The results from the children are given in fig. 1. In the children as well as in the adults the various dipeptidase activities were all significantly lower than those in a control group of nine adult patients with normal mucosa and normal fecal fat excretion.

When the patients were treated with gluten-free diet for some months all the activities increased, most of them approaching the level of those in the control group. The peptidyl-proline dipeptidase activities were, however still decreased.

6 Intolerance to Food Proteins in Malabsorption Syndrome

J K. VISAKORPI

Children's Hospital, University of Helsinki

1) Table 1 presents the incidence and type of gastrointestinal intolerance to food proteins in malabsorption syndrome, according to the series compiled in the Children's Hospital Helsinki (1)

Although eight of the 12 infants with intolerance to cow's milk were also intolerant to gluten in most of them the intolerance to cow's milk was primary Other types of intolerance have also been studied It appears that a patient with intolerance to cow's milk frequently has additional intolerances to many other foodstuffs, such as soya, eggs, meat etc The author has examined an infant with intolerance to cow's milk and beef It seems that gastrointestinal intolerances without malabsorption are rare. No intolerance was observed in 46 children with chronic diarrhoea without malabsorption

2) Diagnosis of intolerance No single test which shows intolerance is in existence The precipitins are unsuitable for this purpose. The only valid method is clinical study As a rule, an improvement in appetite and the cessation of vomiting are the first signs of effective elimination These changes occur 1–2 weeks after the start of elimination Diarrhoea subsides within 1–4 weeks and patients start to gain weight within 3–4 weeks. However absorption tests gave normal results after some months, and jejunal histology after some years. Intolerance may be confirmed by introducing provocation although this is not always necessary moreover it is troublesome, on occasion dangerous, and may provide the wrong result

Usually patients with intolerance to cow's milk rapidly reacted to provocation (in 2–4 hours) with vomiting and diarrhoea nevertheless, about 10–20% of these are slow reactors, which slowly evince symptoms after some weeks of feeding with cow's milk Patients with gluten intolerance usually reacted slowly Less than one half of the cases exhibited an acute reaction, and about 5% of the patients reacted with anaphylactic collapse.

The duration of intolerance to cow's milk is normally rather short, disappearing when the patients reach

TABLE 1 Incidence and Types of Intolerance in Malabsorption

	Infants	Children	Together
Intolerance to			
gluten	12	0	12
cow's milk	28	8	36
together	40	[illegible]	48 (57%)
No intolerance	15	2	17 (20%)
Secondary malabsorption (digestive failure mono- and disaccharide malabsorptions etc.)	10	9	19 (23%)

the age of 7–10 months. The duration of intolerance to gluten is independent of the age. On the average clinically active intolerance lasts 6–12 months, but apparently latent intolerance may remain for life.

The theories which relate to the ethiopathogenesis of malabsorption syndrome with intolerances (celiac disease) are discussed. A hypothesis is presented that there is a primary process, which damages the intestinal mucosa, so that the toxic effect of the gluten-born peptides can act and destroy the structure of mucosa. Subsequently an immunological process against gluten also comes into being. The primary process may be cow's milk allergy, infection, or congenital defect, etc.

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When the patients were treated with gluten-free diet for some months all the activities increased, most of them approaching the level of those in the control group. The peptidyl-proline dipeptidase activities were, however still

It is suggested that the 'atrophy' of villi observed in the mucosa of the patients may count for the low amounts of dipeptidase activities found in these patients

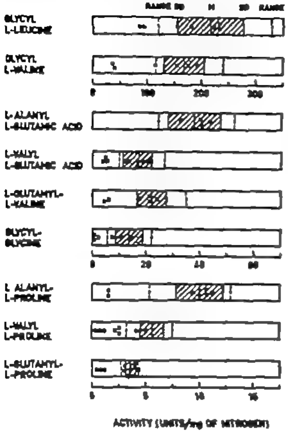

Fig 1 Dipeptidase activities in small intestinal biopsy specimens of the mucosa of flexura duodeno-jejunalis from children with gluten-induced enteropathy ■, from children with regional enteritis and ulcerative colitis □ and from a control group of nine adults with normal mucosa and normal fecal fat excretion ▨ (M=mean value, SD=standard deviation) (3)

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8 Serum Level of Gamma A Immunoglobulin in the Primary Malabsorption Syndrome (Coeliac Disease) in Children

P IMMONEN and J K. VISAKORPI

Children's Hospital University of Helsinki.

Immuno electrophoresis together with the quantitative immuno-diffusion method (1) has been applied in a study of the serum levels of gamma A, gamma G and gamma M immunoglobulins in a series of 126 infants and children suffering from prolonged diarrhoea (3 2)

Pronounced elevation of the gamma A level was encountered in 31 out

of 50 patients with primary malabsorption, and also in 9 out of 14 patients with chronic diarrhoea and malabsorption of unknown aetiology. Hypergamma-A-globulinaemia was infrequent in malabsorption due to defects of digestion, in the secondary malabsorption syndrome, and in patients with normal absorptive function.

It was observable that hypergamma A-globulinaemia was age-dependent in the whole series: it was most frequent, and relatively more marked, in young infants. This was the only immuno-globulin abnormality in more than half of the cases, and was found, together with a less marked increase of gamma-G, in many of the remainder. It displayed no quantitative correlation with the precipating antibodies to cow's milk and gluten. It was almost invariably associated with inflammatory and usually clearly atrophic changes of the duodeno-jejunal mucosa.

In the primary malabsorption syndrome, the level of gamma A closely followed the course of the dietary therapy. During initial treatment with elimination diet, the level of gamma A decreased rapidly and on the average normal levels were reached in 4 weeks. Gamma-A was always normal during prolonged, successful therapy with elimination diet. A re-elevation of the level of gamma-A often followed positive diagnostic provocation (4) with wheat or cow's milk. This was even apparent in the second week after the onset of the provocation; the highest values were observed after three weeks, irrespective of the time at which clinical intolerance became evident, and accordingly of the duration of the provocation. A follow up was made of nine patients on discontinuation of the gluten-free diet. In six of them a marked increase of gamma A occurred. These patients exhibited either no, or only slight, symptoms of intolerance and impairment in the absorption test results although the small intestinal mucosal atrophy was still severe in all five patients subjected to a biopsy.

These findings indicate that determination of the level of gamma A serves as an additional diagnostic test in the primary malabsorption syndrome and is also useful in evaluation of the effect of dietary therapy. The hypergamma A-globulinaemia seems to reflect the inflammatory process of the small intestinal mucosa.

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9 Malabsorption in Patients with Hereditary, Recurrent Cholestasis since Birth

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To be published in Acta Pædiatrica Scandinavica

10 Congenital Primary Hypomagnesemia, an Inborn Error of Metabolism?

D SKYBERG J H. STROMME, R. NESBAKKEN and K. HARNÆS

Department of Pediatrics, and Isotope Division, Department of Clinical Chemistry University of Oslo, Rikshospitalet.

Within the last years, three reports on diseased male infants demonstrating hypomagnesemia as a cardinal sign have appeared (1 2,3) The clinical pictures of these cases have been almost identical and quite similar to that of the male infant reported on here.

Our patient showed generalized tetanic convulsions at the age of four weeks possibly preceded by a period of latent tetany Hypocalcemia (2 6–2 9 mEq/l) and hypomagnesemia (0,5 mEq/l) were found The hypocalcemia was not corrected by calcium treatment alone but upon magnesium medication (initially parenterally later orally) a normalization of serum magnesium as well as of serum calcium occurred Simultaneously the tendency to tetanic convulsions disappeared After the correction there was no need for calcium supplement, but a discontinuation of the magnesium treatment led to a gradual fall in serum magnesium followed by a fall also in serum calcium On the continuous oral magnesium supplement (20 mEq per day) the child has been healthy and has developed normally during 12 months follow up.

In contrast to the three cases reported this one had initially a high serum inorganic phosphorus. Furthermore, repeated determinations of the acid phosphatase as well as the prostatic acid phosphatase in serum have given variable and occasionally very high values. The reason for this remains unexplained. Parathormone given twice while the child was hypomagnesemic and hypocalcemic produced hypercalcemia but no change in the serum magnesium.

As to the possible causes of the low serum magnesium, no underlying disease known to give symptomatic hypomagnesemia, such as gastro-intestinal

diseases, primary aldosteronism or malnutrition has been detected. The observation that the renal excretion of magnesium fell almost to zero (about 0.5 mEq in four days) during a hypomagnesemic period rules out renal leakage as the cause. In fact, studies with radioactive ^{28}magnesium, given orally as well as intravenously indicate that the defect is to be found in an impaired intestinal absorption of magnesium. No significant intestinal loss of endogenous magnesium could be demonstrated.

On the basis of these findings, it appears to us that the child suffers from a congenital selective malabsorption of magnesium. This seems to be a new clinical entity since four cases with almost identical symptomatology have now been reported on.

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SESSION II

CHAIRMAN Jørgen Flamand Christensen Odense

11 A Syndrome with Pancreatic Achylia and Granulocytopenia

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Children's Hospital, University of Helsinki

Cystic fibrosis of the pancreas is the best known disease of the pancreas in childhood In 1964 Shwachman *et al* (2) and Bodian *et al* (1) described a syndrome with pancreatic exocrine insufficiency and hypoplastic bone marrow a disease clearly separable from cystic fibrosis

This is a report on the clinical data of six patients with this new syndrome treated at The Children's Hospital, University of Helsinki. Two of the six were siblings. There was a total of 16 children in the five families affected of these 16 six were diagnosed as having this syndrome four more probably had the disease and six were healthy All the parents were healthy

The patients were all admitted for the first time during infancy they had chronic diarrhoea with failure to thrive (2 patients) diarrhoea, failure to thrive and respiratory infections (3 patients) or respiratory infection only (1 patient) In all five patients absorption tests indicated a malabsorption state typical of pancreatic insufficiency faecal fat was markedly increased, and the xylose excretion test gave a normal finding In all cases, the sweat chlorides were normal. Two patients were subjected to peroral duodenojejunal biopsy (by the courtesy of Dr Kuitunen) and the mucosal histology was found to be normal Pancreatic enzymes in the duodenal fluid were examined in three cases and clearly reduced activities of the enzymes were found Chest x ray did not reveal any fibrotic changes All the patients had variable degrees of granulocytopenia (average 200—400 granulocytes/mm^3) and a clear shift to the left was discovered (mean lobe count 1 49—2 17) Four patients had mild normochromic anaemia. Three of the patients had thrombocyte counts over 150 000/mm^3 and three had counts between 100 000 and 150 000/mm^3 The bone marrow exhibited hypocellularity in two cases, and normo- or hypercellu

larity in four cases. A shift to the left in the myelopoesis was observed in four cases. During severe infections, the number of granulocytes clearly increased in three of the patients.

Two patients who were without infections are now 13 and 14 years old they have steatorrhea and granulocytopenia continuously and their growth is subnormal, but otherwise they are progressing satisfactorily. Four patients died in the hospital of pneumonia, carditis and pneumococcal septicaemia at the age of 6—10 months.

Autopsies on two patients revealed very marked pathological changes in the pancreas. The hypoplastic pancreatic tissue was widely separated by adipose tissue, and acinar cells were almost absent in the hole lobules. The excretory ducts constituted the only component of the exocrine pancreas. The most prominent component in the pancreatic tissue was the cells, of which the structure was largely reminiscent of the islets of Langerhans. The changes were similar but somewhat milder in the two other patients. Some acinar cells were also noticeable in the pancreas of those patients.

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12 Neutropenia and Insufficiency of the Exocrine Pancreas

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This condition was first described by Shwachman *et al* 1963 and has since then been reported by several groups. A review of three relevant materials (1 2 3) gives the following clinical manifestations of the syndrome.

The patients are usually presented during the first year of life, with either severe infections or failure to thrive. They have a variable neutropenia and diminished or lacking excretion of pancreas enzymes with secondary steatorrhea. In addition some patients show short stature, epiphyseal dysplasia or mental retardation. They have normal sweat electrolytes. In some cases siblings have the full syndrome or only neutropenia.

Two siblings (Case 1 and 2) and two unrelated patients (Case 3 and 4) are presented. They demonstrate the different clinical pictures that

can be encountered in connection with this syndrome Efforts have been made to find an immunological abnormality, as the variable or cyclic neutropenia in these patients, with or without pancreatic insufficiency could theoretically be caused by an autoantibody reacting with neutrophils In mouse experiments it was recently demonstrated that polysaccaride antigens from E. coli after a single antigen injection give rise to a cyclical formation of 19 S antibodies (4) Since human blood group antigens, which have been demonstrated on leucocytes, are polysaccarides (5) cyclical neutropenia might be caused by an antibody possibly of the 19 S type

In this communication findings demonstrating that there is in the sera from patients with the syndrome of neutropenia and pancreatic insufficiency cytotoxic antibodies directed against granulocytes

Methods

Granulocytes and lymfocytes were fractionated from blood according to the method of Coulson and Chalmers (6) The presence of cytotoxic antibodies in serum capable of lysing nucleated cells, was examined according to the Gorer and O Gorman technique (7)

Results

In sera from Case No 2 3 and 4 cytotoxicity directed against their own granulocytes but not their lymphocytes could be detected Sera from patients 3 and 4 were also cytotoxic against granulocytes from the father of Case 3 and the mother of Case It has not been possible to obta enough granulocytes from Case 1 perform adequate cytotoxicity tes

Discussion

The cytotoxic factor present in se from these patients is not yet ider tified It has yet to be proved th the factor is of antibody characte Currently sera is fractioned by Se phadex G—200 chromatography determine if the factor is present the gammaglobulin region and if can be characterized as of the 7 S o the 19 S type. Further studies hav to be performed to determine if th factor is of iso- or autoantibody typ We might further speculate that th cytotoxic factor might react wit other cells than granulocytes such a pancreas exocrine cells The familia incidence reported in the literatur and in our cases, as well as the find ings that the patients sera react wit some of their parents sera, suggest that this is a genetically determine disease.

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ABBREVIATED CASE REPORTS

Case 1 2 5/12 year old boy presented at the age of 6 months with failure to thrive and recurrent otitis. Birth weight 2.400 g He is short, following the 3rd percentile. He has severe neutropenia and trombocytopenia. He has a moderate steatorrhea and lacks trypsin in the duodenal fluid. Sweat electrolytes are normal

Case 2. 11 11/12 year old sister of Case 1 presented with severe recurrent otitis from her second year Birth weight 2.400 g She is severely growth retarded — below the 3rd percentile Bone age is not proportionally retarded. Variable neutropenia is present. Duodenal trypsin, sweat electrolytes and chest X-ray are normal. She is slightly mentally retarded.

Case 3. 1 6/12 year old girl with recurrent otitis since the age of 11 months. Birth weight 3.070 g Her height is above the 50th percentile. She has a cyclical neutropenia with peaks of increasing neutrophiles every 16th day She has no clinical or laboratory findings suggesting pancreas insufficiency

Case 4 3 3/12 year old boy presented at the age of 9 months with severe recurrent otitis, once complicated by sepsis. Birth weight 3 760 g Present height is at the 50th percentile. He has a variable neutropenia. He has had periods of frequent loose stools. Pancreas studies have not yet been performed.

13 Intensive Care of Small Premature Infants, Indications and Results of Treatment

E. K. VAPAAVUORI and N G. R. RAIHA

University Children Hospital, Helsinki

Recent reports on intensive care and assisted ventilation of newborn infants include only a few cases of very small prematures. These infants, however are a high risk group with high mortality and with a high incidence of severe RDS The purpose of this paper is to present 56 small premature infants, treated in the Neonatal Intensive Care Unit of University Children's Hospital, Helsinki. All prematures with birth weight between 900

and 1500 g who were admitted to the hospital during the year 1966 are included in the present study

All infants were treated in incubators and skin temperature was maintained at 36 5 C. An umbilical artery was catheterized as soon as possible after admission Arterial pH PO_2 and PCO_2 were determined following a *10* minute period of breathing 90—100% oxygen and after that at frequent intervals. The inspired oxygen concentration was adjusted to maintain arterial PO_2 between 60 and 100 *mm of Hg* The umbilical vein was also catheterized to begin an intravenous early feeding with 10% glucose solution and to correct acidosis by infusing Na bicarbonate according to acid base status.

Intermittent positive pressure respiration (BENNETT respirator type PR I or manual ventilation) was started when 1 primary apnea or repeated apneic spells occurred or when 2 pH PO_2 and PCO_2 could not be maintained.

Of the total 56 cases represented in the table, 31 showed clinical *signs of* RDS and 22 out of the 24 infants requiring endotracheal intubation and assisted ventilation had symptoms of *severe RDS 18 of these* were treated for apnea. 8 were intubated immediately after birth and transferred to the hospital on manual ventilation All had Apgar scores less than 4 at 5 minutes and all expired In the remaining 7 cases the positive-pressure respiration was started when arterial PO_2 and PCO_2 could not be maintained by conservative therapy 4 of these infants survived in contrast to only one surviving of the 18 infants treated for apnea.

The primary cause of death, as demonstrated by gross and histological autopsy findings, was massive intracerebral hemorrhage in 10 of 21 expired cases, total atelectasis of the lungs and severe hyaline membrane disease in 7 pneumonia in 2 and pneumothorax in 2 cases

	Conservative treatment	Respirator treatment	Total
Survived	30	5	35
Expired	2	19	21
Total	32	24	56

The treatment in the two groups designated as "conservative or "respirator" treatment was similar except for the use of artificial ventilation.

14 The Metabolism of Albumin in Normal and Premature Children

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Dept. of Clinical Physiology and Dept. of Pediatrics, Glostrup Hospital, Copenhagen

The metabolism of albumin was investigated in 31 normal children (from 8 days to 13 years old) and in 10 prematures (weight-range 1900 to 2400 g) The results were compared to the findings in normal adults (4)

The metabolic studies were carried out with Behring Werke Human Albumin, trocken, reinst' which we labelled with ^{131}I by the iodine monochloride method of McFarlane (2) In order to block the thyroid gland daily doses of inactive iodide were given orally during the study Each subject received 0.2 μC per kg body-weight of (^{131}I) albumin intravenously The first plasma sample was taken 15 minutes after the intravenous injection, and subsequently plasma samples were taken daily for 10—24 days. The serum albumin concentration was determined immunochemically in each plasma sample by means of the radial diffusion method described by Mancini *et al.* (1) The turnover data were calculated by mathematical analysis of the plasma curve according to Nosslin (3) The final slope of the plasma curve was controlled by whole body counting

In prematures and infants the serum albumin concentration was lower and the plasma volume/kg body weight was higher than the corresponding values in bigger children and adults. The intravascular mass of albumin/kg body weight was of the same order of magnitude both in children and adults (c. 2g/kg) Consequently the low serum albumin concentration in the smallest children is merely due to dilution.

The fractional catabolic rate (per cent of intravascular albumin mass degraded per day) decreased from about 20% in the prematures to about 8.5 / in the bigger children and adults. Correspondingly the rate of synthesis was high in the prematures (c. 0.50g/kg/day) and infants (c. 0.32 g/kg/day) compared to the bigger children (c. 0 17 g/kg/day) and adults (c. 0 16 g/kg/day)

Finally a good linear correlation was found between the rate of synthesis (g/day) and body weight, regardless of age.

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3. Nosslin, B, cited in S. B. Andersen, Metabolism of Human Gamma Globulin. Blackwell, Oxford, 1964, p. 115.

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15 The Q—A_2 Interval during Exercise in Assessing Severity of Aortic Stenosis

F GYULAI and Z. WALSH

Department of Pediatrics, Karolinska Sjukhuset, Stockholm

The patient material consists of 8 controls (2 normal 6 with minimal right sided involvement) and 14 patients with congenital aortic valvular stenosis (5 with gradient < 35 mm Hg 7 with gradient > 35 mm Hg 2 with clinical findings of mild AS) Both selective angiocardiography and cardiac catheterization were performed in all except 2 of the cases. Recordings were taken from the right second intercostal space with a 4-channel jet writer at a paper speed of 100 mm/sec. at rest and during exercise on a bicycle ergometer with a gradually increasing work load until the pulse rate reached 170—180 beats/min Each Q—A_2 value was the mean of at least 5 determinations

Fig 1 shows that at rest (supine) there was no significant difference in duration of the interval plotted against heart rate in patients and controls. However throughout exercise (sitting) at a comparable increase in

The relationship between Q A2 time and heart rate at rest in supine position in children with cong aortic stenosis

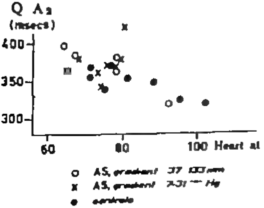

Fig 1

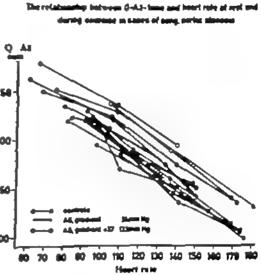

Fig 2

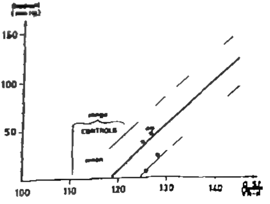

Fig 3.

heart rate, patients with more severe aortic stenosis had longer Q—A_2 intervals (Fig 2) This relationship was further demonstrated by the highly significant correlation found between the interval (corrected for heart rate) and the gradient across the aortic valve ($y = -562 + 4\ 75\ x$, $p < 0\ 001$) A similar relationship between the interval and left ventricular pressure was noted.

Work supported by grants from the U.S. Public Health Service (1 T O 1 HD 166—01 American Heart Association and Association for Aid to Crippled Children).

16 Deficiency of β-galactosidase and α-mannosidase — Primary Enzyme Defects in Gargoylism and a New Generalized Disease?

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It has been known for some time that mucopolysaccharides and gangliosides accumulate intracellularly in the lysosomes in patients with gargoylism. This storage may possibly be explained by a deficiency of a lysosomal enzyme, β-galactosidase. When the activity of several lysosomal acid hydrolases was measured in tissues, a deficiency of β-galactosidase was found in the liver skin and brain in patients with Hurler's syndrome and in the skin in patients with Hunter's syndrome Other lysosomal enzymes, including β-glucosidase, β-glucuronidase, N-acetylglucosaminidase, acid phosphatase, α-glucosidase, cathepsin C, α mannosidase α-fucosidase and β-xylosidase had a normal or higher than normal activity in the tissues. The deficiency of β-galactosidase did not seem to be due to the presence of an inhibitor

Increased activities of several acid hydrolases, including β-galactosidase, were found in the plasma in patients with Hurler's and Hunter's syndrome.

The possibility is discussed that there is a relationship between the low activity of β-galactosidase and the etiology of gargoylism.

A patient presenting a clinical picture resembling Hurler's syndrome was also studied. He had a marked tendency to infections, mental retardation, coarse traits, resembling Hurler's syndrome, hepato-splenomegaly gibbus, abnormality of the vertebrae, small grey patches on the capsule of the lens, hypogammaglobulinemia, vacuolized lymphocytes and storage cells in the bone marrow He died at the age of 4½ from an infection. Marked storage of a PAS-positive substance was found in the nervous system.

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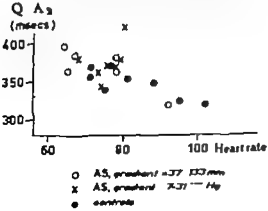

Fig 1

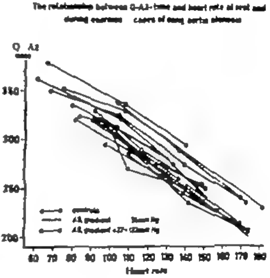

Fig 2

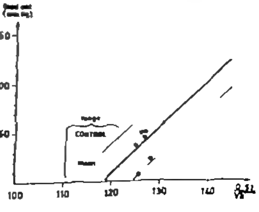

Fig 3.

18 The Diagnostic Value of Peripheral Venous Angiocardiography in Newborns and Young Infants

M. DAHL, L. HIRVONEN, E. KOIVISTO T PELTONEN and P VUORINEN

Children's Hospital and the Cardiorespiratory Research Unit of the University of Turku, and the Department of Radiology of the University of Oulu

Catheterization of the heart and intracardiac angiocardiography is not always possible in newborns and young infants. The authors have therefore studied the possibility and diagnostic value of peripheral venous angiocardiography in the diagnosis of congenital heart defects.

Peripheral venous angiocardiography was performed in 37 newborns and young infants. The contrast medium was injected into the vena premalleolaris.

In 27 cases the contrast was good and in 4 cases sufficient for a diagnosis. The failure in 6 cases at the beginning of the series was caused by various technical errors.

The contrast was good in the following cases 4 cases of ASD 11 cases of VSD 3 transpositions of the aorta, 3 coarctations of the oarta, 2 cases of pulmonary stenosis and 3 cases with a normal heart. The contrast was sufficient for the diagnosis in the following cases 3 cases of ASD and 1 case of VSD

A large transseptal shunt diminished the contrast considerably in some cases.

Peripheral venous angiocardiography can be recommended as a quick and comparatively reliable method for the examination of congenital heart defects in newborns and young infants, if catheterization of the heart or intracardial angiocardiography is not possible.

20 Premature Activation of Bilirubin UDP-Glucuronyl Transferase

A. F BAKKEN

Pediatric Research Institute, University of Oslo, Rikshospitalet

Conjugated bilirubin is normally not present in the serum of newborn infants. However in heavily Rh-immunized infants the presence of conjugated bilirubin ... veral times already at birth. This situation has been called obstructive jaundice in infants suffering from erythroblastosis foetalis. Evidence of ob-

This patient was found to have a storage of a mannose-containing substance, not yet characterized in the brain and the liver The activity of α mannosidase was low in the liver spleen and brain while several other lysosomal acid hydrolases were more active than in the controls.

The possibility is discussed that this patient represents a new disease with a deficiency of α mannosidase and consequent storage of a mannose containing compound

17 Nursing Ability of Norwegian Mothers

A. KÅSS

Department of Pediatrics, Vestfold Central Hospital, Tønsberg

At Vestfold Central Hospital we have examined the nursing ability of 2000 mothers of healthy full term babies When discharged from the obstetrical department 82% of the mothers gave full breast feeding 13 7% gave partial breast feeding whilst only 4 3% were discharged with artificial food for the baby

A follow up based on questionaries that also included various social information showed that the duration of the nursing ability was dishearteningly short.

Whilst more than 95% gave breast at their discharge this number fell to 50% already after 7 weeks 28% after 3 months and 12% after 6 months. Whilst 82% had full nursing ability at their discharge this number is reduced to 50% even before one month had gone and after 3 months only 15% of all mothers had full nursing ability Mothers who were discharged thus had only 50% chance of the same status after one month s time.

The duration of nursing showed no sure relationship to the mother s age or to the number of pregnancies On the other hand there seemed to be a slightly increased duration of the breast feeding in mothers from the countryside and in mothers from the financially best situated groups.

The material confirms the findings of other authors. The mothers of our time have good ability to establish breast feeding but a total lack of ability to keep up the good status promised by the amount of milk in the puerperium.

Should it be possible to expect improvement in this connection a radical change of opinion must occur with in all medical bodies and the public Measures that can be applied during pregnancy in puerperium at the obstetrical department, and during the critical period following discharge to the home, have been discussed

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jugated bilirubin has not been found in these cases.

The existence of conjugated bili rubin in the serum of an infant is however primarily an indication of the bilirubin UDP glucuronyl tran ferase (BGT) being activated in the infant, as the conjugated bilirubin is unable to pass the placenta If conjugated bilirubin is present in an in fant at birth the BGT must have been activated prematurely

In cases of premature activation of the BGT the conjugated bilirubin will accumulate in the fetus and thus infant will present the symptoms of obstructive jaundice.

Infants suffering from erythroblastosis foetalis have been investigated It was found that the most immunized infants developed the ability to con jugate and excrete bilirubin earlier than the less immunized infants

Bilirubin itself was postulated to be the trigger of the BGT and the conjugated bilirubin to be the trigger of the capacity to excrete the bilirubin from the liver cell to the biliary capillaries

Three clinical groups were proposed

Group A Both the conjugating and the excretory capacities activ ated after birth (Normal and slightly immunized infants.)

Group B The conjugating capacity activated before birth and the excretory capacity activated after birth (Heavily immunized infants.)

Group C Both the conjugating and the excretory capacities activated before birth (Infants suffering from hydrops foetalis)

Pregnant rats were loaded with bilirubin and it was shown that the offspring of these rats were able to conjugate bilirubin at birth in con trast to normal newborn rats.

21 Globin as a Transport Protein for Bilirubin

J FOG E. KJELDSBERG and A. F BAKKEN

Pediatric Research Institute, University of Oslo, Rikshospitalet

In electrophoresis at pH 7 two yel low proteins have been observed in icteric sera from the newborn one which moves as bilirubin albumin and one which moves as a complex formed from bilirubin and globin This led to the assumption that globin acts as a transport protein for bili rubin

A colourless globin was prepared from hemoglobin and renatured as described by Lemberg and Legge (1) This globin contained traces of por phyrin and therefore, probably also

of iron. That the globin was in its native form was ascertained by adding alkaline hematine and sodium dithionite whereby the absorption curve of hemoglobin appeared. The absorption curve of oxyhemoglobin was registrable after oxygenation.

Alkaline bilirubin, added in excess to the globin and run on a Sephadex G-25 column with a phosphate buffer pH 6.2 (I 0.05) gave two yellow fractions, one nearly stationary due to free bilirubin and one which moved with the protein. The spectral absorption curve of the globin fraction was similar to the curve usually obtained with protein bonded bilirubin.

Electrophoresis was performed on strips of cellulose acetate and Krebs—Ringer's phosphate solution at pH 7.0. The anode was placed in pure phosphate buffer and linked to the system by cotton to avoid evolution of free chlorine. Icteric sera from cases of erythroblastosis and prematures which contained only unconjugated bilirubin, separated in two yellow fractions in this system, one which followed the albumin towards the anode and one which moved towards the cathode in the same way as bilirubin-globin formed in vitro. This yellow globin band was more pronounced in prematures. The albumin fraction reacted with diazotized sulphanilic acid while neither the cathodic fraction from icteric sera nor the complex formed from bilirubin and globin reacted on the strip even if it was treated with ethanol.

Globin would seem, taking into account its origin, and the above findings to function as a transport protein for bilirubin while the bilirubin albumin complex must be a store of bilirubin separated from globin but still unconjugated.

A bilirubin-iron-globin is a reasonable metabolite in hematoglobin degradation. A ring structure of the tetrapyrrol with the metal in the middle as in the structure given for the zinc biliverdin complex (2) and linked to the imidazol of the globin may explain why the complex fails to react with diazotized sulphanilic acid even in the presence of the usual accelerators.

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22 Subsepsis Allergica Wissler

G BERGLUND and G WESSNER

Department of Pediatrics, Children's Hospital, Gothenburg

Subsepsis allergica or Wissler's syndrome is characterized by intermittent fever, exanthema, arthralgia, serositis, leucocytosis with eosinophilia.

The Children's Hospital in Gothenburg has during 1959—66 treated 12 patients with the diagnosis Wissler's syndrome. All were less than 10 years of age There were as many boys as girls

The first symptom in 9 cases was prolonged remittent fever in 3 cases combined with exanthema and arthralgia. The onset in 3 cases was insidious with diffuse joint symptoms and/or skin manifestations All patients had remittent fever and atypical exanthema during the course of the disease. 10 patients had joint symptoms, mostly short lasting and a few *had periarticular oedema. Serositis* developed in 5 usually pericarditis but also pleuritis and possible engagement of the peritoneum.

Laboratory findings high sedimentation rate, leucocytosis predominantly granulocytes but no eosinophilia The platelets showed high values in most cases. In some cases the number of platelets was correlated to the course of the disease Blood cultures were negative Antistreptolysin titre in 10 examined cases showed no increase. Antinuclear factor was negative in 8 cases examined Immunoglobulins examined in 3 cases were without changes Gammaglobulins were increased in 3 cases.

The 9 patients in whom fever was the dominating first symptom were first treated with antibiotics, without effect.

The joint symptoms were not influenced by salicylates or phenylbutazon.

Steroid treatment (prednisolon) gave an immediate effect in 11 patients, in a dose of 2—3 mg/kg body weight initially and with a slow decrease. If treatment was diminished too rapidly relapses occurred sometimes necessitating long treatment (more than 1 year) In 4 of these 6-merkaptopurine was tried with uncertain result.

Relapses appeared in a few cases several years after freedom from symptoms *without therapy The symptoms* were mainly the same as earlier but appeared to be less severe — possibly on account of more promply started therapy (prednisolon)

The prognosis is fairly good 1 patient expired 9 months after the onset of the disease, having received steroid treatment for 8 months At autopsy fresh bleedings in the adrenal cortex as well as chronical fibrotic pericarditis, slight diffuse interstitial fibrosis of the myocardium and pleuritis were shown No vasculitis or collagenosis was demonstrated

Differential diagnoses in high fe

brile cases were usually sepsis, osteomyelitis or febris rheumatica but the negative blood cultures, the lack of endocarditis and the negative antistreptolysin titre excluded these diagnoses. Those with dominating joint symptoms were difficult to distinguish from rheumatoid arthritis, but they demonstrated shifting polyarthritis, and no chronic changes or deformities developed.

SESSION III

CHAIRMAN Docent Jan Winberg Göteborg

23—31 Round Table Conference on Non Obstructive Urinary Tract Infections in Children

Participants H J ANDERSEN T BERGSTRÖM, L. Å. HANSON K. LINCOLN A. NYEGAARD F ORSKOV and I ØRSKOV

32—33 Free Lectures

Chairman Mr President esteemed collegues.

When discussing urinary tract infections (UTI) in childhood I think it may be wise to keep the following in mind We cannot disregard the possibility — not to say the probability — that many adults now straining our resources for chronic dialysis or renal transplantation have their renal damage as a consequence of renal infections during childhood. Our diagnostic and therapeutic possibilities as well as our knowledge of symptomatology have improved considerably during the later years. The doctor of today therefore has a much heavier responsibility for these patients than his somewhat older colleague who lacked many of today's facilities.

With regard to this we will concentrate the talk today on diagnosis, symptomatology and therapy As an illustration of this you will see here at the table three bacteriologists, two immunologists and three pediatricians. (The roentgenologist was alas unable to participate today)

In a stenciled paper that you will find on your desks we have tried to summarize our points of view upon the practical management of UTI and will let the discussion here be an illustration of that paper Dr Lincoln will first give you some bacteriological aspects.

K Lincoln To secure the diagnosis of urinary tract infection it is necessary to determine the species and the quantity of the infecting microorganisms. 262 first infections in girls were caused by *E coli* in 91 per cent, by *Klebsiella*, *Proteus* and *Pseudomonas* in 5 per cent and by enterococci in 1 per cent. In 81 recurrent non-obstructive infections in 20 girls the corresponding figures were 80 5 and 14 per cent. Thus bacterial etiology does not seem to be quite similar in first and recurrent infections.

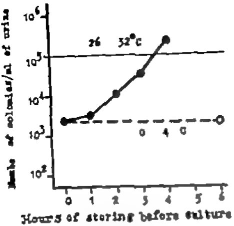

Fig. 1 Change of bacterial number of *E. coli* in urine stored at different temperatures.

stored at 26—37° C
stored at 0—4°C

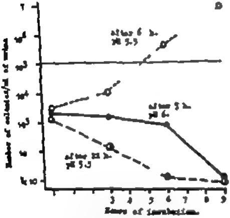

Fig. 2. Change of bacterial number of *E. coli* at 37° in three urine positions obtained at different times after single oral dose of shortacting sulphonamide (sulfisoxazole, GANTRISIN) of 50 mg/kg body weight. Even 22 hours after ingestion of this small dose urine contained enough sulphonamide to inhibit bacterial growth.

Urine obtained 5, 22 and 61 hours after ingestion of sulphonamide.

The figure of Edvard Kass from 1954 of 100 000 colonies per ml of urine is still valuable as a rough borderline between contamination and infection. We want again to emphasize the great importance of 1) proper cleaning before voiding, 2) immediate culture or cooled transport of the urine (Fig 1) and 3) the necessity of omitting therapy during a sufficiently long period before culture. (Fig 2) If quantitative culture is impossible, other methods of estimating bacterial quantity must be tried microscopy of stained smears of urine or chemical tests. In 222 urine samples from girls a tetrazolium test (Uroscreen) gave correct positive result in 79 per cent (69/88) and correct negative result in 89 per cent (119/134) when compared with 100.000 col/ml on quantitative culture.

As regards sulphonamide sensitivity we found in 237 first infections in girls that more than 90 per cent of the strains were sensitive. In 82 recurrences only 32 per cent were sensitive. It is thus impossible to generalize about the sensitivity pattern

The presence of pyuria was dependant on the clinical type of infection, see below

Chairman These things are simple but fundamental, and I will especially underline how erroneous it may be to cultivate urine not cooled during transportation.

E. coli is the dominating etiology in UTI. We know of the existence of enteropathogenic strains. Are there also special uropathogenic strains? This has been studied in a material of first infections in girls.

TABLE I

	Göteborg		McGeachie (Scotl.)		Kunin (USA)	
Strains	First infection	Recurrent infection	First infection	Recurrent infection	First infection	Recurrent infection
Groups	152	258	182	134	95	76
		%	%	%		%
01	9	11	12	4	5	9
02	22	8	8	3	2	7
04	13	10	14	9	3	8
06	7	6	13	14	13	5
07	14	4	3	2	7	12
08	1	5	1	1	—	—
018	8	5	3	1	—	—
075	1	3	5	10	6	8
8 0 groups Total	75	52	59	44	36	49
01 — 0148	92	83	—	—	67	71

F og I Orskov (WHO International Escherichia Centre, Statens Serum institut, Copenhagen Denmark)

By biochemical and serological analysis it is possible to subdivide *E coli* strains into thousands of stable types.

The first and most simple step in this analysis is the determination of the 0 antigen 148 different *E. coli* antigens are known to-day Using antisera corresponding to these antigens, it is possible to determine the 0 group of 80—90 per cent of coli strains isolated from urinary tract infections. Some 0 groups (1 2 4 6 7 8 18, 75) are more common than others by the use of antisera corresponding to these eight antigens it is possible to determine the 0 group of 50—75 per cent of urinary strains Table I

With only few exceptions the same 0 groups are found to be frequent in urinary infections in different parts of the world Any coli 0 group can be found among sufficiently large numbers of urinary or faecal strains. Comparative investigations of faecal and urinary strains have shown that the same 0 groups are frequent in the intestine and in the urinary tract. At this juncture it should be stressed that too little is known about the distribution of *E coli* serotypes in the normal intestinal flora. Few if any of the hitherto published materials are quite satisfactory for a comparison between 0 group distribution among urinary strains and intestinal coli strains Nevertheless most investigators have found that the concentration of a limited number of 0 groups is greater in urine than in faeces, in other words it is possible by the use of the above mentioned eight 0 group antisera to determine the 0 group of a higher percentage of urinary strains than of faecal strains.

In Table I the result of a comparative investigation of urinary coli strains from first and recurrent infections in children is recorded For comparison the data from related in

vestigations in Scotland and USA have also been included. The Gote borg and the Scottish material both show a tendency to greater concentration of the 8 common 0 groups in the first infection material compared to the strains from recurrent infections. On the other hand, Kunin's examination does not show this tendency

We can conclude

1) The same coli 0 groups are common in urinary infections and in faeces, and the same common 0 groups are found in children and in adults.

2) The common coli 0 groups are found relatively more frequently among urinary strains than among faecal strains.

3) Some investigations — including the present one — show a tendency towards a greater concentration of these same 0 groups in first infection strains, compared to strains from recurrent infections.

4) Thus the situation is drastically different from that of the so-called enteropathogenic coli serotypes which are only found in children and primarily in sick children in children's institutions.

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2 Calvin M Kunin, Robert Deutscher and Albert Paquin Urinary Tract Infection in School Children. An Epidemiological, Clinical and Laboratory Study *Medicine* 43 91 1964

Chairman Several investigations have demonstrated that only a minority of children hospitalised with UTI are referred with a correct diagnosis. Thus many doctors seem to be unfamiliar with the symptomatology A certain system in the variable clinical picture may be obtained by relating symptoms to such factors as sex, age, first infection or recurrent infection, which we will illustrate by three groups of patients.

T Bergström I will demonstrate some observations we made in girls aged 2 months — 16 years concerning the difference between first and recurrent infections.

There is a great risk of overlooking recurrences since they are often asymptomatic or give only vague symptoms. It seems as if the rate of asymptomatic infections is highest among the girls with many earlier infections. Thus, in a group of 100 girls with their first recurrence the ratio symptomatic to asymptomatic infections was 3:2 whereas in another group of 82 girls with repeated UTI the same ratio was 2:3

Further the urinary white cell count may be an unreliable diagnostic aid in recurrent infections. Whereas pyuria is found in almost 100 per cent of first infections it is often lacking in recurrent infections. Thus out of 130 recurrences caused by coliform bacteria only 2/3 had a urinary white cell count exceeding 50 cells per mm³ The corresponding figure for recurrences caused by enterococci was 1/3

Some doubt seems to exist about the danger of asymptomatic bacteriuria, especially when not combined

TABLE 1

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06	7	6	13	14	13	5
07	14	4	3	2	7	12
08	1	5	1	1	—	—
018	[illegible]	5	3	1	—	—
075	1	3	5	10	6	8
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In Table 1 the result of a comparative investigation of urinary coli strains from first and recurrent infections in children is recorded For comparison the data from related in

with pyuria. But let us look at Figs. 3 A—C demonstrating the course of the disease in a girl followed from her first infection. In Fig. 3A only the symptomatic infections are presented and I do not think that many doctors would be alarmed by such a history. If the asymptomatic recurrences are added, Fig. 3 B, the situation appears a little more serious. The i.v. pyelography is plotted in Fig. 3 C and you should notice that scarring took place during a period dominated by asymptomatic recurrences. Such observations, which are not unique, underly our definite opinion that asymptomatic infections should be diagnosed and treated. Dr. Andersen will soon give you another illustrating example.

Chairman: From these observations we can thus conclude that the more frequent the recurrences, the more difficult the diagnosis — symptoms and white cells may disappear. A plausible explanation for this may be the development of tolerance to endotoxin.

Now over to nonobstructive UTI in boys, which is a rare disease after the first year of life — we found a sex ratio ♂/♀ of about 1/20. How do they appear clinically?

H. J. Andersen: We found 27 first or second infections in boys 4—15 years old. Some data are collected in Table 2.

It is obvious to anyone that this picture is not the same as that found in first infections of girls, and maybe the pathogenesis is also different? The relative infrequency of fever, of *E. coli* in the urine and the slow return of

TABLE 2

Some clinical characteristics of 27 boys aged 4—15 years with their first (22) or second (5) known UTI. No roentgenologically demonstrable obstruction.

Dominating symptoms	
Fever	11
Abdominal pains	14
Macroscopic haematuria	7
Laboratory findings	
Microscopic haematuria	9
Concentration capacity lowered (often with slow restitution)	17
I. V. Urography	
Parenchymal reduction	5
Dilation of calyces.	4
	9
Bacteriology	
Coliform bacteria	10
Proteus	8
Staph. albus	5
Enterococci	3
Klebsiella	1

the concentration capacity to normal is suggestive of chronic pyelonephritis — using the word in its anatomical meaning. The parenchymal reduction demonstrated by x-ray in several of these patients may support this idea. So perhaps one should not mix boys and girls — at least not when discussing UTI.

Chairman: Neonatal infection is the third type of UTI which we want to discuss. From a study of 76 such infections (onset 0—30 days) not complicated by roentgenologically demonstrable malformations the following can be concluded:

Sluggishness, feeding difficulties, irritability, tenderness upon touching, poor gains in weight have been repeatedly described as leading symptoms.

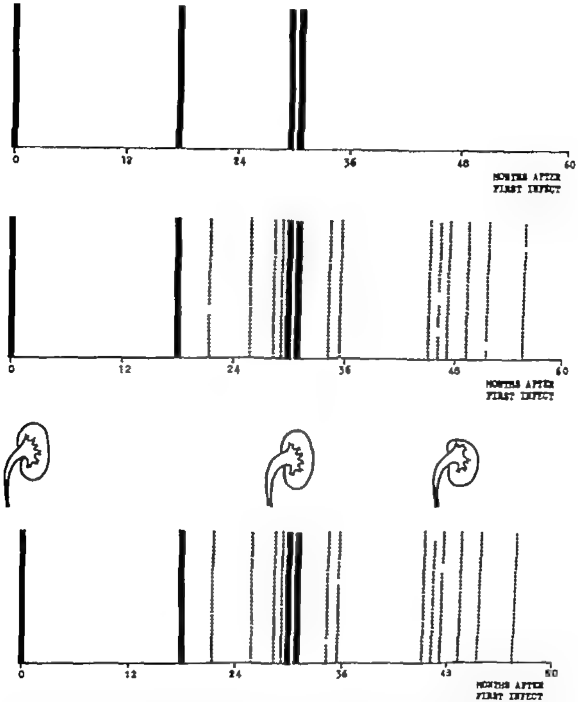

Fig 3 M.M. 540716 — a girl followed from her first known UTI at the age of 5 years
A. Only symptomatic infections plotted. This history does not seem especially alarming
B. The asymptomatic infections also plotted. The picture looks a little more serious. During the "free" interval between 36 and 46 months there was no check up, nor treatment.
C. Consecutive urographies show progressive scarring. This seemed to be especially rapid during a period dominated by asymptomatic infections.

Symptomatic infection

Asymptomatic infection

TABLE 3.

63 04 14 U J		Afebrile infections last year. Sulfonamide (Gantrisin) July 27—Aug 29. Nitrofurantoin Sept 7—16. No symptoms during observation period.			
1968	E. coli per ml	Leucocytes per mm³	Conc. cap. mOsm/l	ESR	Coliantibodies titre
30.8	Neg	80	540	7	2^9
1.9	1 Mill	5000			
3.9	1 Mill	320			
12.9	Neg	29	440	41	2^{15}
21.9			560	45	

Table 3 shows the application of these methods in a patient with an asymptomatic recurrence, with onset during hospital stay

Chairman This illustrates again that the asymptomatic infections may be severe and deserve our close attention. Check up cultures are necessary

Turning to the question of therapy it is essential to know the resistance pattern of the infecting bacteria. Again no generalized answers can be given — the resistance pattern varies among different patient groups. We can, however expect more than 90 per cent of first infections in girls to be sensitive to sulphonamide. Thus there is, for the moment, no reason to abandon this drug in first infections in girls. But for how long should the patients be treated?

T Bergström We treated 134 first infections in girls for 10 days and 103 for 60 days with Gantrisin, a short acting sulphonamide. A thorough follow up for one year showed a frequency of recurrence amounting to 33 per cent and 31 per cent respectively Thus nothing seems to be gained by extending therapy to 60 days in girls with first infections. This material will soon be published in detail (Acta Paediat Scand)

Chairman If we now turn our interest to the nature of recurring infections there are two possibilities either they are new infections, i.e. new invasions of the urinary tract, or they are recrudescences of an earlier defectively healed infection.

T Bergström We investigated this in 20 girls with 82 recurrences and found the frequency of new infection to be between 70 and 85 per cent. From this we can conclude that therapy had eradicated the infection in most instances, but failed to prevent new ones.

In patients with an established inclination to repeated infections long term *profylaxis* with a small dose of sulphonamide may reduce the frequency of recurrence. In contrast to this patients with a true chronic infection (i.e. bacteria persisting in the renal parenchyma) require high doses of bactericidal substances over long periods. These points of view are dealt with in *J Ped. 71* 13 1967

In children consecutive measurement of kidney growth is an indis-

This is true but in our experience other symptoms often triggered our attention towards the possibility of an UTI namely weight loss > 10% of body weight, a typical grey colour or cyanosis, distended abdomen simulating ileus and CNS symptoms not due to meningitis. It should be pointed out that fever and increased sedimentation rate was not a usual sign A positive blood culture was found in 50 per cent of those investigated markedly increased blood urea nitrogen in about 20 per cent. One third had massive reflux up into the calyces These infections seem to be as severe as they are difficult to diagnose Thus it was a not unusual experience that urine findings were negative for several days after the onset of symptoms

As you have noticed from the presentation of these three groups of patients the clinical picture and the laboratory findings vary with the type of the clinical material

The next speaker will touch upon some of the important urological aspects

A Nyegaard (in collaboration with T Gerts and M Eiken)
Since 1963 all children admitted to Gentofte Hospital with recurrent pyuriae have been included in a prospective study with special emphasis on radiography and surgical examination for evaluation of indications and results of operative treatment.

A preliminary report is given of the prevailing symptoms and results of long term medical treatment

Of a total of 66 children admitted in the years 1963 to 1966 19 were boys and 47 girls. Only 2 of the 26 children under 1 year had a completely normal X ray at the first examination 12 had hydronephrosis, 4 mega ureteres with reflux, and 3 had duplications in the urinary tract. A total of 16 of these children had various operations performed

Of 40 children more than 12 months old at first examination 19 had no abnormalities in the urinary tract. 7 had hydronephrosis, 4 mega ureteres and 3 had duplications in the urinary tract. 11 children had various corrective operations performed.

In follow up of these patients interest has been concentrated on whether the uretero-pelvic reflux could be secondary to urinary infections, in which case it would disappear during medical treatment of the pyuria. This seems to be the case in a few instances but the reverse causality seems to be the most common and at the time being a number of these patients have been re admitted for consideration of surgical measures against the reflux. The outcome will be reported when sufficient time has elapsed for evaluation of the results.

Chairman It seems reasonable to evaluate a pyelonephritis as a more severe infection than a cystitis. It is therefore a pertinent task to determine the anatomical location of the infection.

H J Andersen A description of two methods determination of renal concentration capacity and of the *E. coli* antibody titre, which both well serve this purpose has been published in detail (*Acta Paediat Scand 48* 318, 1959 *idem 54* 247 1965)

of existing methods for demonstration of bacteria by chemical methods.

Second Most recurrences in unobstructed infections are *not* due to inef fective treatment. Consequently interest should be directed more to better methods for profylaxis than to new ones for treatment. Long term check up is as essential as treatment of the acute infection.

Third Some patients develop a chronic disease others remain healthy as regards the kidneys. One of the most important goals for research now is to find methods by means of which those threatened by chronic disease can be recognized early For the moment it is for the sake of these relatively few that we have to check all patients for many years.

32 The Long Term Prognosis of Non-Obstructive Urinary Infection in Childhood

B. S. LINDBLAD and K. EKENGREN

Department of Pediatrics, Kronprinsessan Lovisas Barnsjukhus, Stockholm

107 of the cases of children with non obstructive urinary infection, hospitalised during the years 1940—49 fulfilled the criteria of urinary in fection suggested by Steele *et al.* (1) 76 of the boys and 70% of the girls were reinvestigated.

At the time of reinvestigation the boys showed neither progressive renal disease in the form of parenchymal reduction nor infection and had not been treated for any urinary infection during the observation time.

Non-obstructive urinary infection in girls seems to be a potentially serious disease In spite of sulpha-treat ment late symptomatic recurrence had occurred in half of the cases. In 40% of the girls with late recurrence, or 19 % of the total, progressive upper urinary disease could be demonstrated Early recurrence, mentioned in the primary report, increased the risk of progressive renal disease from 4 to 30% After 20 years observation time, a single thorough clinical investigation, if negative, is not sufficient to evaluate the patient's condition. Besides repeated X ray investigation a thorough anamnesis seems to be of the greatest importance in the case of urinary infection in both children and adults.

It appears possible from the reinvestigation that maximal dehydration during pitressine load can provoke recurrence in recurrent or latent infections. In two additional cases, being treated in this clinic for recurrent infections from 6 months of age, it was

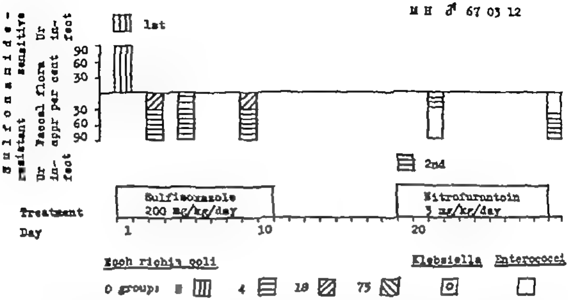

Fig 4 Change of aerobic faecal flora during oral sulphonamide (Gantrisin) treatment. The faecal flora was dominated by sulphonamide sensitive 02 at the first UTI During sulphonamide treatment there was a rapid change of the faecal flora. *E. coli* 02 vanished and sulphonamide-resistant 04 and 018 became dominant. When this patient got a recurrent infection at 19 days this was caused by the *E. coli* dominating at that time — namely sulphonamide-resistant 04

pensable method of ascertaining therapeutic effect (HODSON)

Chairman In one of our studies recurrences appearing immediately after the interruption of sulfonamide therapy were caused by sulphonamide resistant bacteria in 95 per cent (21/22 cases) The traditional evaluation is *defectively healed infections due to* selection of resistant strains in the urinary tract. But can we be sure of that?

K Lincoln (in collaboration with G Lidin Jansson) As most of the recurrent infections are true reinfections with new strains, the *site of development of resistance to* sulphonamide is probably not the urinary tract but rather the intestinal tract, see Fig 4

Chairman Finally we will discuss the situation where *we are* rather sure of a UTI but the urine findings are persistently negative.

H J Andersen Such situations may be the consequence of obstruction micro- or macroscopic, or presence of chemotherapeutic substances in the urine. Another possibility may be the occurrence of spheroplasts — *the cell wall-deficient forms of* bacteria. In these instances determination of the *E coli* antibody titre may be of diagnostic aid (cf *J Ped* 67 1080 1965)

Chairman Concluding this conversation I want to say the following *First* We have to sharpen our diagnostic accuracy as far as our resources permit Urine culture is the superior method for demonstration of bacteria, but for those who lack this possibility I will hope for a further improvement

of existing methods for demonstration of bacteria by chemical methods.

Second Most recurrences in unobstructed infections are *not* due to ineffective treatment. Consequently interest should be directed more to better methods for profylaxis than to new ones for treatment. Long term check up is as essential as treatment of the acute infection.

Third Some patients develop a chronic disease, others remain healthy as regards the kidneys. One of the most important goals for research now is to find methods by means of which those threatened by chronic disease can be recognized early. For the moment it is for the sake of these relatively few that we have to check all patients for many years.

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It appears possible from the reinvestigation that maximal dehydration during putrescine-load can provoke recurrence in recurrent or latent infections. In two additional cases, being treated in this clinic for recurrent infections from 6 months of age, it was

possible to provoke bacteriuria during maximal dehydration although there had been no symptoms and negative cultures for up to the previous 15 months. High diuresis during the treatment of acute pyelonephritis and a pitressine load in combination with urinary quantitative culture when checking the effect of the therapy is suggested

REFERENCE

1 STEELE, R. E. LEADBETTER, G W and CRAWFORD J D Prognosis of childhood urinary-tract infection. *New Engl J Med*, *17* 883 1963

33 A Follow Up Study of 101 Patients with Infection of the Urinary System

(*Material stretching over a period of 5 years after 12—16 years of observation*)

T-O ENDSJØ

Department of Pediatrics, Ullevål Sykehus, Oslo

During the period 1950—1954 101 patients were hospitalised at the Children s Ward, Ullevål Hospital with different forms of infection of the urinary system. Of these 85 were girls and 16 boys. Most of them were treated with sulfonamides for 5—7 days, and a few for some time longer until their urine was normal. According to the present point of view the necessity for subsequent regular control was at that time not sufficiently emphasized

In 1966 a questionary was sent to each patient inquiring amongst other things whether the patient had had infections of the urinary system or other diseases of the urinary system All the patients filled out the questionaries. It appeared that 35 considered that they had later had a relapse of infection of the urinary system 66 considered that they had not had any infection of the urinary system after their first day at the ward On later examination it was seen that 4 of these had pyelonephritis.

Before their first hospitalisation, 58 children had had pyuria more than once. 28 were of the opinion that they had had infection of the urinary system during the period of observation 30 considered that they had suffered no relapse The follow up study showed that 3 of these had pyuria.

Of the 35 patients who according to the questionary considered that they had had infections of the urinary system during the observation period, 25 submitted to a follow up study The usual clinical tests were made urography and in about half the patients urethrocystography The tests

showed the following results X ray of 5 patients showed pyelonephritic changes, 5 had hydronephrosis, 1 patient had died on account of renal failure 2 years after the first hospitalisation in the ward. Follow up studies were also carried out on 14 patients who considered themselves as having been without relapse during the observation period 11 of these had recurrent pyuria before the first hospitalisation and 3 had malformations in the urinary system. Urography of the 3 patients with malformations showed pyelonephritic changes. One of these had pyelonephritic changes at the first examination One patient had clinical pyelonephritis and 10 patients showed no signs of infection of the urinary system. Of all the patients undergoing follow-up studies, it was considered necessary to hospitalise 10 for further investigation.

Urography was carried out on 87 children during their first stay in the ward. 62 of these had a normal urography 20 had malformations, 5 had hydronephrosis. Of the 14 patients who had not been tested with urography there were none who according to the questionary considered that *they had later had* a relapse of their infection of the urinary system. Out of 62 patients with normal urography at the first examination, 21 stated that they had later relapses of urinary system infection. Among the 20 children with malformations in the urinary system, 14 were found to have had relapses of urinary system infection Of 5 children with hydronephrosis, 2 were found to have had relapses.

Only 2 out of 9 patients with pyelonephritis and 5 with hydronephrosis had come for regular examination after their first hospitalisation in the ward. Considering these findings there is all reason to emphasize the necessity for regular control of children with malformations in the urinary system.

Even with one single attack of pyuria and normal urogram, the chances for relapse of infection of the urinary system seem to be so great, that there is all reason to convince both patient and parent of the importance of subsequent medical control.

SESSION IV

CHAIRMAN Ole Wasz Höckert, Uleåborg

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34 Subnormal Concentration of Urinary Glucose as A Sign of Urinary Tract Infection in Children

B. SCHERSTÉN H FRITZ and L. KÖHLER

Department of Clinical Chemistry Department of Medical Microbiology and Department of Pediatrics, University Hospital of Lund

Urine from healthy fasting individuals contains small amounts of glucose. In adults the normal range has been found to vary from 2 to 20 mg/100 ml of urine A level below 2 mg/100 ml of urine was found to be a reliable indication of significant bacteriuria (1) This finding seemed to offer opportunities for mass screening for bacteriuria This communication reports the results from such a screening of 511 school girls aged 7—18 years.

METHODS

The children were instructed to empty their bladder on going to bed They were not allowed to eat anything after that time but were permitted to drink up to one glass of water during the night They were instructed not to urinate until the morning The urinary samples were collected as mid stream specimen from the first morning urine The samples were immediately chilled in a plastic ice bag and delivered to the school nurse in the morning The samples were sent to the laboratory for glucose determination and bacteriological culture The urinary glucose was determined by a fluorometric automated method using the fluorescence developed from $NADPH_2$ in relation to the amount of glucose in the sample in the presence of hexokinase glucose-6-phosphate dehydrogenase and NADP Significant bacteriuria was considered to be present when two or more samples collected consecutively showed growth of more than 100 000 organisms per ml of urine

RESULTS

Fig 1 shows a histogram of the urinary glucose concentrations found in 511 school girls.

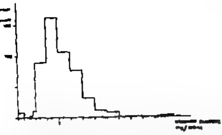

Fig 1 Distribution of urinary glucose concentration in 511 school girls 7 to 18 years of age.

In table 1 the correlation between urinary glucose and significant bacteriuria is evaluated. In eight girls there were less than 1 mg of glucose/100 ml of urine. Seven of these subjects had significant bacteriuria. The remaining subject showed no bacterial growth when cultures were made by routine method from two samples collected during a period of 3 weeks. When however cultures from the same samples were set up on a high osmotic medium, bacterial L-forms (protoplasts) were found. On subcultures these L-forms reverted to classical *E coli*

TABLE 1 Evaluation of subnormal levels of glucose in urine as sign of significant bacteriuria in 511 school girls.

[illegible]	Significant bacteriuria	No significant bacteriuria	Total number of cases
[illegible]			
[illegible]		503	503
[illegible]		[illegible]	511

x Including one subject with heavy growth of bacterial L-forms.

In the group of 503 subjects with more than 1 mg of glucose/100 ml of urine one girl had more than 100 000 *E. coli* in both samples collected These two samples, however had been collected in her chamber pot. The third sample, collected under appropriate conditions showed no bacterial growth. In the same group 10% of the girls had growth of 1 000—100,000 organisms per ml of urine. In

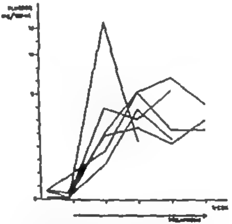

Fig. 2 Urinary glucose concentration before and after treatment in 6 subjects with significant bacteriuria. (In one of the subjects the second urinary glucose value before treatment is missing)

the second sample most of them showed no bacterial growth and still normal urinary glucose more than 100 000 organisms per ml of urine were not found in any one subject.

Fig 2 shows the effect of treatment on the urinary glucose concentration in six of the eight girls with significant bacteriuria. It may be seen that the normal range of glucose is found already in the sample collected after treatment for one week.

Thus the determination of urinary glucose seems to be a good screening method for significant bacteriuria as in this material all seven subjects with bacteriuria were detected Furthermore, one subject with bacterial L-forms was found None of the 503 subjects with normal urinary glucose had significant bacteriuria according to the criteria given

Mass screening for potentially serious diseases requires, however simple methods. For that reason we have developed a paper test sufficiently sensitive to react with the small amounts of glucose normally present in urine (2)

TABLE II Relation between colour reaction of test paper B and glucose content of 386 urinary samples.

Glucose content g/100 ml	Number of sample	TEST [illegible] REACTION AFTER [illegible]			
		No colour		++	+++
	2				
	8				
1					
3 [illegible]	[illegible]				
Total	386				[illegible]

In table II some of these results are summarized All 12 samples with less than 1 mg of glucose per 100 ml of urine gave no colour reaction with the test paper All these samples were collected from subjects with significant bacteriuria Out of the remaining 374 samples with more than 1 mg of glucose per 100 ml of urine and without significant bacteriuria, 2 gave no colour with the test paper and all the others a positive reaction for glucose Thus the sensitivity of the paper to detect significant bacteriuria was 100% and the specificity e.g the ability of the test paper to disclose non significant bacteriuria, was 99%

SUMMARY

In a material of 511 school girls 1.5% were found to have significant bacteriuria. All these cases could be detected by a sensitive automated fluorometric method for determination of urinary glucose as cases with significant bacteriuria have subnormal levels of urinary glucose (< 1 mg/100 ml) A glucose specific test paper is described, sufficiently sensitive to react with the small amounts of glucose normally present in urine The test paper can be used to discriminate between urinary samples containing less than, and those containing more than 1—1.5 mg of glucose per 100 ml of urine. Thus, the test paper may also be used as a screening method for significant bacteriuria.

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35 Roentgenology and Micturition Dynamics of Infants with Urinary Tract Infections

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At the Clinic of Pediatric Surgery in Gothenburg we have made 150 simultaneous measurements of intravesical pressure and urine flow in children with recent urinary tract infections. 29 of the patients were infants. Our purpose has been to evaluate quantitatively an obstruction to flow suggested by the micturition urethrocystogram.

The material is chiefly composed of cases with urethral valves and bladder neck obstruction. In roentgenological terms, a valve means a distal urethral obstruction with distinct restriction of the lumen and change of urethral shape. In the bladder neck region, the obstruction is not so clearly defined. The anomaly of shape is expected to be of great importance as a cause of restriction to the urinary flow In the frontal and oblique as well as lateral projections there are sharp edges or bars in the bladder neck region instead of a flow promoting funnelshaped bladder urethra junction (Contraction coefficient) The enlargement of the diameter of a tube can increase the turbulence, thereby reducing the flow Other important factors are the length of the tube as well as the location of the obstruction in the proximal or distal urethra.

The intravesical pressure has been measured with a suprapubically introduced catheter in connection with a pressure transducer the urinary flow with a vertically mounted pressure transducer connected to an electronic derivator Pressure, flow urine volume, rectal pressure and detrusor pressure (rectal pressure subtracted from intravesical pressure) have been simultaneously recorded.

It is not possible to calculate correctly the minimal resistance to flow at a micturition because the urinary flow is laminar as well as turbulent in character We have been searching for an expression, called r with the same characteristics as resistance to flow So far we have been using the equation

$$r = \frac{P}{(Q\ k)^2}$$

where P is intravesical pressure, Q urinary flow and k a correction factor whereby flow is transformed to flow per square meter body surface area.

The following facts have been shown

1 Correlation between roentgenological and hydrodynamic evaluation is good.
2 In 6 cases, where the X ray films were suggestive of bladder neck ob-

struction, the pressure flow measurements yielded low (normal) values for r No operative procedures were performed in these cases. Further examination has shown the same or lower r values parallelling improvement of the roentgenological signs of obstruction.

36 Bacteriological Screening during the Neonatal Period

G BERGQVIST and J KJELLANDER

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Infections are considered to be responsible for 10—20% of all perinatal mortality and currently afflict at least 1‰ of all newborn The symptoms of neonatal septicemia are diffuse which is probably one reason why the mortality rate is as high as 30—70% i.e about the same as from septic shock.

Neonatal septicemia, which appears during the first 72 hours of life, has normally been acquired before or during delivery and is caused principally by the coli group and by enterococci. Certain factors, such as a long time lapse between rupture of the amniotic membranes and partus, high temperature in the mother at delivery prem maturity and operations, increase the risk of infection Earlier investigators studied the relationship between infections in infants and positive blood cultures from the umbilical cord and histological changes in this If both of these factors existed a high percentage of the infants developed a septicemia. Infants with a positive blood culture from the umbilical cord have been reported to show signs of infection in 15% of cases, frequently containing the same bacteria strain

As this method seemed simple and not particularly laborious, we have cultured blood from the umbilical cord as a routine measure in all cases of complicated delivery in order to obtain a small risk group — subsequently thoroughly examined and when signs of infection were found treated according to the resistance pattern from the culture Early and adequate antibiotic treatment is effective in reducing the high mortality rate in neonatal septicemia.

From Oct 16, 1966 to May 31 1967 1 444 infants were born and in 160 cases blood cultures were taken from the umbilical cord The majority of the positive cases were regarded as contaminations as it is difficult to wash this region and contaminations are common even in normal delivery whereas staf aureus, e coli coliforms, enterococci, proteus and pseudomonas were regarded as suspectedly

pathogenic and the infants in these cases were reexamined with new blood cultures, quantitative urine cultures, throat cultures, micro-sedimentation rate and white cell blood count. Out of 20 infants thus examined, 3 had a clinical septicemia, although not verifiable upon cultivating check specimens. These infants were treated and survived. Three other infants had already received adequate prophylactic therapy.

This method appears valuable as a screening procedure, although we were unable to ascertain whether or not the strain found in blood from the umbilical cord is the same as that which produces symptoms.

37 Studies of Glykose Tm in Predominantly Unilateral Nephropathological States

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38 Studies of Aldosterone Excretion in Renal Hypertension

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39 Polyneuropathy in Children

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In the presented 42 children below 16 years of age impaired function could be demonstrated in at least two peripheral nerves The material was primarily divided according to the presence or absence of findings indicating involvement of the central nervous system also Thirteen children showed signs of such involvement whereas 28 appeared to have only peripheral neuropathy and in one case occurring in a newborn infant with severe muscular hypotonia and areflexia this point could not be settled

Among the 13 children with involvement also of the central nervous system two had late infantile metachromatic leucodystrophy one had a severe neurological complication to rubella with symptoms from the brain the spinal cord and the peripheral nerves, and two had Friedreich's ataxia. Several cases could not be assigned to any special group Three patients had an acute reversible disease reminiscent of a Guillain Barré syndrome, in two of them complicated only by definite reversible electroencephalographic abnormalities and in one by a severe brainstem involvement with unconsciousness lasting for three weeks. One boy had cerebellar ataxia and convulsions Another boy had a primary myopathy besides evidence of involvement of both the central and the peripheral nervous system. Three patients showed progressive symptoms, in two of them, two brothers the clinical picture was reminiscent of that described under the heading of chronic Wernicke-encephalopathy and in the third child clinical and laboratory findings were typical of Krabbe's disease.

Among the 28 children without signs of involvement of the central nervous system 11 had diabetes mellitus. These 11 were found among 107 unselected diabetic children who were studied in order to find the incidence of peripheral neuropathy in juvenile diabetes mellitus Two patients had a classical Guillain Barré syndrome A positive family history was recorded in 12 cases, occurring in eight different families The clinical picture varied in this group from minimal findings to severe, handicapping muscular weakness and wasting The findings in different affected members of the same family were similar whereas the variation was great between different families In three patients no explanation for the polyneuropathy could be found They all run a protracted course similar to that of the hereditary cases. In one of the unexplained cases the clinical findings were confined entirely to the right median nerve, but extensive neurophysiological examination revealed involvement of all examined peripheral nerves.

In the patients without involvement of the central nervous system the most common clinical findings were slow clumsy movements, muscular weakness and wasting, particularly of distal muscles, and hypoactive or absent muscle reflexes. Increased spinal fluid protein was seen in about half of the patients in whom this examination was performed. Decreased conduction velocity was noted in practically all the patients electro-myographical signs of denervation of distal muscles were seen in many of them.

40 The Librium Analogue Mogadon in the Treatment of Epilepsy in Children

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All diazepin derivatives in clinical use have some anticonvulsive properties. This also applies to chlordiazepoxide hydrochloride (Librium[R]) itself but its anticonvulsive effect is too limited to make it clinically useful. Valium[R] (7-chlor-benzodiazepin) has already gained a legitimate place as an antiepileptic drug of recognized importance, the main indication being all types of status epilepticus, where an intravenous injection of 2—10 mg in most cases gives a dramatic effect within one minute. The author has tried a third derivative, Mogadon (nitro-benzodiazepin) in 35 children with different types of minor fits which are often a much larger problem than major seizures.

The doses used in most cases ranged between 0.5—1.0 mg per kg body weight per day The tablets are of 5 mg each. Mogadon was found to be useful in more than half the cases with minor motor seizures (15 children) earlier resistant to numerous other anticonvulsants. Two infants with infantile spasms with no or only partial response to ACTH became quite free from seizures. Excellent results were also obtained in about one fourth of 15 cases with psychomotor epilepsy Some other cases benefited to a lesser degree. In the rest of the cases the effect was nil, or only transient. Two teen-age girls with a myoclonic type of genuine petit mal could be kept free from fits, while the result in 3 cases with the ordinary type of petit mal was poor

The side effect usually consisted of drowsiness, ataxia and the provocation of grand mal, the last mentioned occurring in 6 cases. Four children, three of them less than 3 years old, developed a rattling breathing with a marked bronchial hypersecretion. In a further two cases, a copious hypersalivation was observed, one of them also had increased lacrimation

about half an hour after each tablet of 5 mg A pronounced increase in appetite and weight was noted in 6 children One girl aged 14 attempted suicide after 17 tablets of Mogadon à 5 mg She developed severe ataxia, was drowsy and slightly confused, but her respiration was never depressed and she was all the time in a good general condition

41 Syndroma Gilles de la Tourette

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Gilles de la Tourette described in 1885 a syndrome starting in childhood and characterized by multiple motor tics coprolalia and often also by echolalia and echokinesis. The condition usually begins below the age of ten and is more common among boys than among girls The first symptoms are motor tics affecting the head face and neck The tics are violent in nature and noticed first when the patient is tired excited or under stress Gradually the symptom free intervals become shorter and the trunk muscles and legs become involved As the disease progresses vocal tics develop usually described as barking or grunting The last phase, which is said to be characteristic for the illness, is coprolalia utterance of obscenities Because of the often desperate outcome of the illness as well as the vigorous motor symptoms, many authors hold the opinion that the syndrome is based on a brain damage whose nature however is not known Symptomatic remissions, often on psychotherapy have been reported since 1940 Eisenberger Ascher and Kanner (1959) offered as their opinion that it seems justifiable to treat the patients psychotherapeutically Such treatment may at least be beneficial to the child and his family in overcoming the social handicaps brought about by the illness. In addition to this it is to be hoped that it may diminish the intrapsychic tensions which aggravate — if not cause — the symptoms.

Faux (1966) reported a case, whose complete recovery was attributed to three years treatment in a specific therapeutic hospital milieu where the patient in a new and meaningful way became able to comprehend some of the basic interpersonal problems.

Since 1961 a few cases have been published in which chlorpromazine seemed to alleviate symptoms and at least five cases have become symptom free on haloperidol

At the Pediatric Clinic of the University of Turku three cases of the syndrome under study have been found from 1965 to 1967 All are boys

from nine to twelve years of age. In one of the cases the prognosis seems to be very poor the patient cannot attend school, and repeatedly runs away and hides in the forests. His motor tics and echolalia are very prominent.

The second case is a boy of ten whose motor tics and loud shrieks had developed within the last year before admittance to the hospital. The boy had been under observation at a neurological ward, where his neurological examination and EEG were found to be normal. The boy is the youngest of five. His father is a jailer and his occupation may have coloured his opinions on bringing up children. The mother is a very submissive woman who tries to minimise the father's orders and prohibitions. Three of the boy's siblings have been antisocially disturbed. At the hospital the boy was first very restless and continuously uttering a loud "hah hah" This patient improved considerably in a pediatric ward where milieu therapy was given. The doctor (Dr Antti Kumento) who was in charge of the ward had a warm and acceptive relationship with the boy and this seemed to have a specific therapeutic value. *The boy's symptoms* first disappeared in situations where he experienced a safe feeling of being together with the doctor Behind the boy's restless and aggressive behaviour a strong need for tenderness was to be seen. As medicinal treatment the boy was given 30 mg Truxal daily His improvement has been sustained for at least half a year

The third patient is a boy of ten who developed symptoms typical of syndroma Gilles de la Tourette at the age of four after having been shut up in a dark wardrobe by mistake. At *the age of six, he had a symptom-free* interval for several weeks but his symptoms re-appeared after his mother went away for a two days trip This boy's symbiotic but aggressive clinging to his mother seems to be a central problem. In addition to these psychological problems the boy may be suffering from a brain damage caused by a long and difficult delivery His present neurological examination and EEG are normal but his psychological tests show disturbances characteristic of diffuse brain damage. The boy and his mother have been on out patient psychotherapy once a week for three months and the boy has been on haloperidol, 2 mg daily for two months. During the treatment his condition has improved considerably echolalia and coprolalia have disappeared and motor tics now appear in a very mild form.

The aetiology of Gilles de la Tourette's *syndrome* may be thought of as being multidimensional The organic and psychological factors form a spectrum of causation and their relative impact varies from case to case It is possibly that this condition is specifically connected with repressed aggressive emotions. The lessening of aggressions might lead to the disappearance of the symptoms. The improvement attributed to haloperidol may possibly also be connected with this, as haloperidol is usually indicated in aggressive, *manic* and psychomotor agitation.

43 Studies of the Incidence of Preputial Adhesions, Phimos and Smegma, among Danish Schoolboys

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To be published elsewhere

44 Effect of Physical Training on School Children with Severe Motor Handicaps

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17 students at the Norrbacka Institute Schools. Cerebral palsy (CP) in 7 cases (median age 19 years) and para plegia from other causes than CP in 10 cases — mostly myelomeningocele — (median age 17 years) All students have severe motor — but not mental — handicaps and use wheel-chairs during their daily activities.

The students have been physically trained during 30 minutes twice a week for 6 weeks, parallel with the ordinary gymnastic lessons at school The training consisted of fast wheel chair driving raising and heaving up and down on the arms in the wheel chair and at the parallel bars, train ing with iron bars and heavy balls.

Submaximal work loads for all the students and maximal work loads for 8 non CP students were performed on an ergometer bicycle for arm work - Identical submaximal wor loads were performed before an after the training period togethe with determinations of oxygen uptake heart rate, blood lactate concentra tion and roentgenological heart vo lume.

A lower concentration of blood lac tate was found after the training in the CP group In the paraplegia group the oxygen uptake heart rate and blood lactate showed significantly lower values after the training In none of the groups could a change in heart volume be detected

The 8 students in the paraplegia group who could perform maximal work had increased this about 40% after the training

The better training results in the paraplegia group could be explained by the more severe handicap in the

CP-group, where also the arms were affected in most cases in contrast to the paraplegia-group The heart rate during training averaged 140 beats/min in the latter group but only 115 beats/min in the CP-group

The results show that these severely handicapped adolescents were capable of improving their working capacity in spite of the fact that the training was of rather mild intensity and performed during a relatively short period Thus, the ordinary gymnastic lessons seemed to be inadequate in order to improve the student's working capacity and should be changed to involve a training programme of the above described type. A higher working capacity is highly desirable for these students with regard to their performance in school and during their activities of daily living

It is concluded that this type of training should be included in the conventional habilitation programme for children and adolescents with motor handicaps of this type.

45 Infant Health Visitors as Collectors of Statistical Material

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The Danish public health visiting service, which was legalized 30 years ago is based on the infant health visitors going to the homes.

Thanks to this the health visitor contacts practically all homes having babies, notwithstanding the economical and social status of these and she will thus be able to make a personal contribution by collecting statistical material to form an estimate of the normal child's growth and development, or by registering the presence of various abnormal conditions among the children.

As the health visitor goes to practically all homes with babies the investigations are not beset with the same uncertainty as if only a certain section of the population had been under consideration.

Besides this, the training and social attitude of the health visitors gives them the best opportunity of avoiding a merely schematic conception, as for instance the evaluation of housing conditions solely according to the number of rooms etc.

In this connection it is of value to know that the health visitor thanks to the natural relationship of trust between her and the mother will be able to obtain far more reliable information than for instance professional interviewers would procure. In fact several of the investigations would

hardly have been practicable without the assistance of the health visitors.

In order to obtain as correct information as possible the health visitor's observations in the home are supplemented by information from hospitals or out patients clinics where the children have been examined, just as in cases of death of children information is obtained from a post mortem examination, if this is conducted

When health visitors assist in special research programs questionnaires or case records are made for the purpose

Finally the health visitor can in certain cases assist in actual experiments, just as the information on the standard sheet can serve as a source for comparative follow up-examinations, for instance, when the child reaches school age.

Reliable results of statistical research however depend on careful consideration of a lot of factors, not only during preliminary and statistical operations, but also in the final clinical — statistical evaluation of results.

As conclusions could be stated

1) The material must be as comprehensive as possible so that random variations will not have a decisive influence on results.

2) The material ought to be representative, and if it only comprises parts of a population-group the selection must be made in such a way that it is a completely casual section a random sample

3) The desired information must be tabled in well-defined groups, and the person taking down the information must be carefully instructed in order to avoid wrong classifications.

4) The information ought, when possible, to be supplemented from other sources, for instance by information from hospitals, etc.

5) In statistical research work there must be a close collaboration between the doctor and the statistician to avoid untenable or even directly wrong conclusions.

SESSION V

SUBJECT Growth Disturbances

CHAIRMAN Henning Andersen, Copenhagen

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46 Hormones and Growth

H. ANDERSEN

Children's Hospital, Fuglebakken, Copenhagen

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47 Pituitary Dwarfism

M. SEIP

Department of Pediatrics, University of Oslo, Rikshospitalet

To be published in greater detail in Archives of Disease in Childhood

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48 On Human Growth Hormone

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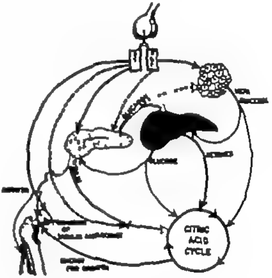
Human growth hormone prepared according to the method of *Roos et al* (5) (here called HGH) had somatotrophic activity and a potent adipotrophic, hypocalcaemic and hyper glycaemic effect in rabbits Removal of a lipid mobilizing factor (LMF) from the crude human pituitary ex tract before preparation of growth hormone yielded a more homogene ous somatotrophic hormone (STH) On a per weight basis the somatotrophic activity of STH was about 25% higher than that of HGH The lipotrophic effect of STH was negli gible and it had no hypocalcaemic or hyperglycaemic effect in rabbits (6) The LMF was a potent adipotrophin in the rabbit and in man in rabbits it induced a prolonged hypergly caemia and a hypocalcaemia, with convulsions and death following big doses (7)

Ultracentrifugation studies demon strated that HGH is a mixture of STH and a lipid mobilizing fraction the molecular weight of STH being calculated to be about 18 900 (1) while *Li et al* (3) gave a molecular weight of 21 500 for human growth hormone Subcutaneous injection of 5 mg STH into 6 rabbits gave a mean increase of serum non-esterified fatty acids of $0\ 55 \pm 0\ 03$ meq/l ($\pm$ s e) while 5 mg hydrolyzed STH into 3 rabbits gave a mean increase of 1 54 $\times 0\ 05$ meq/l *Laron* (2) observed in creased in vitro lipolytic effect of STH after proteolysis

A dualistic effect of growth hor mone was discussed designated somatotrophic hormone (STH) and pituitary diabetogenic factor (PDF) in the Figure.



The LMF has no somatotrophic activity either biologically or im munologically (7) and immunization of rabbits has not produced LMF antibodies. However the immuniza tion produced a potent STH anti serum (4)

It was suggested that a lipotrophic core might be built into the amino acid-chain which forms the growth hormone similar to a MSH which forms a part of the ACTH-chain Pi tuitary enzyme systems may split off this core or the whole growth hor

mone depending on the demand of the organism. If this core is antigenic, it yields a good explanation of the observed increase of growth hormone in adult serum during variations in stress and in requirements for energy from fat depots. The LMF may itself be a new pituitary adipotrophin.

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49 Chromosomal Abnormalities and Short Stature in Gonadal Dysgenesis

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In 1954 different groups of workers demonstrated that the majority of patients with Turner's syndrome were sex chromatin negative, and in 1959 Ford and his coworkers (1) reported X-*chromosome monosomy* in such a patient. Recent cytogenetic findings have brought about a redefinition of Turner's syndrome as a syndrome of X-chromosome monosomy or partial monosomy with subsequent gonadal dysgenesis. Short stature is the most constant clinical finding in Turner's syndrome. The other somatic abnormalities might be present to a various extent, but might also be completely absent. The absence, or presence in only a slight degree, of phenotypic manifestations has especially been noted in cases where the X monosomy has been present in mosaicism, but is also now and then seen in cases with clear cut X *monosomy*.

In attempts to correlate the clinical to the cytogenetic findings cases with structural anomalies on the X-chromosome have been especially informative. These structural anomalies in

clude X isochromosomy for either the long or the short arm deletions of the long or the short arm of the X chromosome, and mosaics with these anomalies in one of the cell lines. Based on the findings in own and published cases with such structural anomalies Ferguson–Smith and co-workers (2) have concluded that the short stature and other somatic effects of Turner's syndrome can be produced by the loss however caused of the short arm of the X-chromosome only whereas the gonadal dysgenesis can be produced by the loss of either arm The findings in patients with deletions of the X-chromosome without mosaicism have particular significance in testing the validity of these conclusions. However such cases are rare, and hitherto only one patient has been reported with deletion the short arm (3) and a total of cases in which the deletion involv the long arm (4 5 6)

Two additional patients are repor ed one had a deletion involving t short arm of the X-chromosome ar the other a deleted long arm In bot patients the clinical findings were agreement with those expected accor ing to the hypothesis of Ferguson-Smith *et al*

Case I X. G J The patient was first se at the age of 14 years because of short statur The pregnancy was uneventful and she w born at term. The birth weight was abo 2000 g. Her motor and mental developme were normal. Although her general healt was good, she showed slow weight gain an linear growth from birth.

Her height was 132 cm (15 cm below 2.5 percentile) and her weight was 39 4 kg (3.

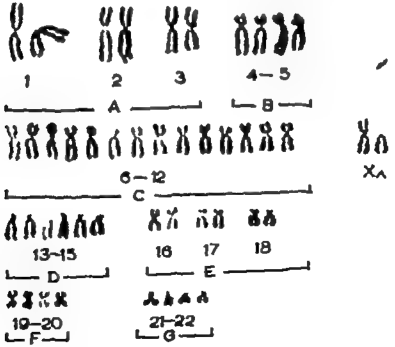

Fig 1 Karyotype analysis in case 1 showing a deletion of the short arm of one X-chromosome.

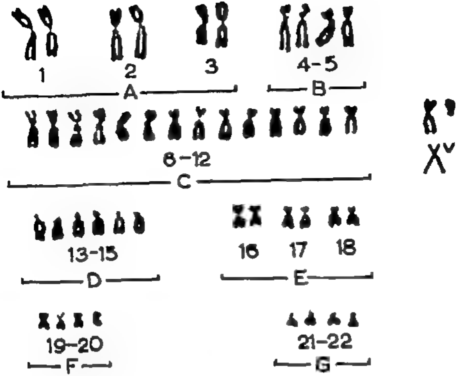

Fig. 2. Karyotype analysis in case 2 showing a probable deletion of the long arm of one X-chromosome.

kg above 97.5th-percentile). Her body build was rather stocky but the proportions corresponded to the chronological age. The neck was short, without webbing. There was bilateral cubitus valgus. The breasts were infantile with widely spaced nipples. Axillary hair was absent and pubic hair very sparse. Gynaecological examination revealed infantile female external genitalia. The uterus was small and ovaries were not felt. Exploratory laparotomy revealed bilateral streak gonads. The gonadotropin excretion in the urine was less than [illegible] M.U. per 24 hours.

Cytogenetic investigations. Buccal and vaginal smears revealed 10–12 per cent sex chromatin positive cells, but it was noted that the sex chromatin body was smaller than usual. Chromosomal analysis was carried out in cultured leucocytes from peripheral blood. A total of 90 metaphases were examined. Eighty six contained 46 chromosomes. Twenty of these cells were analysed in detail. In each instance the karyotype contained only 15 chromosomes in the C group and 7 chromosomes in the D group (Fig. 1). In view of the clinical findings and the small size of the sex chromatin body the extra chromosome in the D group was interpreted as a X chromosome with a deletion involving most of the short arm.

clude X isochromosomy for either the long or the short arm, deletions of the long or the short arm of the X chromosome, and mosaics with these anomalies in one of the cell lines. Based on the findings in own and published cases with such structural anomalies Ferguson—Smith and co-workers (2) have concluded that the short stature and other somatic effects of Turner's syndrome can be produced by the loss, however caused of the short arm of the X-chromosome only whereas the gonadal dysgenesis can be produced by the loss of either arm. The findings in patients with deletions of the X-chromosome without mosaicism have particular significance in testing the validity of these conclusions. However such cases are rare, and hitherto only one patient has been reported with deletion of the short arm (3) and a total of 3 cases in which the deletion involved the long arm (4 5, 6.)

Two additional patients are reported one had a deletion involving the short arm of the X-chromosome and the other a deleted long arm. In both patients the clinical findings were in agreement with those expected according to the hypothesis of Ferguson—Smith *et al*

Case I A. G J The patient was first seen at the age of 14 years because of short stature. The pregnancy was uneventful and she was born at term. The birth weight was about 2000 g Her motor and mental development were normal. Although her general health was good, she showed slow weight gain and linear growth from birth.

Her height was 132 cm (15 cm below 2.5th percentile) and her weight was 39 4 kg (5.4

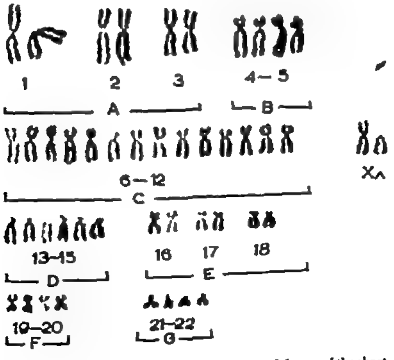

Fig 1 Karyotype analysis in case I showing a deletion of the short arm of one X-chromosome.

50 Skeletal Development as a Measure of Biological Development

E. ANDERSEN

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The estimation of skeletal age has become increasingly common as a measure of biological age both in transverse and longitudinal examinations.

In Denmark no systematic investigation of skeletal development has previously been made. The present study was completed in 1964 and involved a transverse examination of 1009 Copenhagen school children aged 7—18 years. The skeletal age was compared with chronological age, height and sexual development. It was of particular interest to investigate the children during adolescence because of the large range in development during this period.

Several methods of estimating skeletal age exist. In Scandinavia Elgenmark has developed a method which can be used only with children aged 0—5 years. The skeletal age of the present material was estimated according to the American atlas of Greulich and Pyle (1). The English system of Tanner and Whitehouse (2) was also applied. In this latter method the stage of development of 20 selected bones in the hand and wrist is rated on a scale of 8 (in one case 9) possible stages. Each bone *is awarded points* according to its stage of development. These points are totalled for the 20 bones and reference to a table gives the skeletal age. The later stages of carpal bone development cannot be reliably placed on the scale. Their point system is calculated in such a way that a difference of one stage in rating of a single carpal bone in older children would give rise to a difference of up to 2 years in the skeletal age estimation. A revision of the points system will probably improve the method which is, however rather time consuming to use.

Greulich and Pyle's atlas is easier and quicker to use. The present investigation has shown that this atlas can be applied to Danish children from 7—18 years of age provided that a correction of 6 months is made. Thus the average Danish boy of 12 years will have a skeletal age estimated from Greulich and Pyle's atlas of 11½ years. The American sample from which the atlas was constructed had matured under the highest socio-economic and cultural conditions and this may explain the 6-month retardation of the Danish children. The SD of the skeletal age estimation was 12 months on the present Danish material.

The skeletal age estimated by Greulich and Pyle's atlas was compared with the height and sexual development. There was a significantly higher correlation between skeletal age and height, and menarche, development

Case 2 T R. The patient was seen at the age of 20 years because of primary amenorrhoea and sexual infantilism. She had always been healthy No menstruations had occurred.

She was a rather tall girl with slightly enuchoid body proportions. Her height was 176 cm and her weight 73 kg There were no anomalies suggestive of Turner's syndrome. The breasts were undeveloped. Axillary and pubic hair were present, although somewhat sparse in the pubic region. The external genitalia and clitoris were infantile. The urinary gonadotropin excretion was 83 I U per 24 hours. An exploratory laparotomy revealed an infantile uterus and both ovaries were whitish and very small (streak gonads) Microscopical examination of biopsy specimen from the right gonad showed a fibrillious tissue without evidence of germinal epithelium or germ cells.

Cytogenetic investigations Very tiny sex chromatin like masses were present in 7 per cent of buccal mucosal nuclei Chromosomal analysis was performed on two separate occasions, both in cultured leucocytes from peripheral blood A total of 140 metaphases were examined One hundred and thirty six contained 46 chromosomes. Fifty seven cells were analysed in detail. Each metaphase contained only 15 chromosomes in the C group One chromosome which could not be paired had an acrocentric appearance and the size was about the same as an E chromosome. (Fig 2) This chromosome was tentatively identified as a X-chromosome with a deletion involving most of the long arm although the morphology resembled that of the Y-chromosome. However the evidence against this being an Y-chromosome was presence of tiny sex-chromatin like masses, absence of any testicular tissue and clinical and cytogenetic findings which were in accordance with those reported previously in cases with deleted long arm of the X-chromosome (4 5 6.)

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increment measurements are presented. Sex differences are found in many of the measurements. Boys are significantly taller than girls up to 4—5 years of age and have significantly larger heads and bicondyles up to the age of 7. Regarding weight the boys are significantly heavier only up to 2 years of age. The subcutaneous tissue of girls is significantly thicker than in boys from 3 years and upwards. The subcutaneous tissue of both boys and girls is markedly increased during the first months of life but later decreases. At about five years of age the subcutaneous tissue again increases in girls but not in boys.

Diagrams for distances and increments in height, weight and head circumference are presented for use in clinical work.

52 A Longitudinal Study on Skeletal Maturation in Healthy Finnish Children up to Five Years of Age

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The Finnish longitudinal growth study project, which was started in 1953 includes a yearly determination of the skeletal age of the children at their birthdays. The present preliminary report is based on a material of 85 children who have reached the age of five years, 36 boys and 49 girls. Socio-economically they represent the middle class Helsinki population. The methods of Elgenmark and Tanner—Whitehouse have been used, the former being based on a Swedish and the latter on a British child material.

The skeletal maturation of Finnish and Swedish children was found, on the average, to correspond well. Compared with British children, Finnish girls showed no differences from British girls, whereas Finnish boys had a consistently higher skeletal age than British boys at corresponding ages.

Of genetical factors affecting skeletal maturation the influence of sex was again clearly evident already at the age of one year the overall score for the girls was significantly higher than for the boys, which means that maturation of individual bones was more advanced in girls. Another apparently genetical factor was the stature of the parents. When those children whose skeletal age at five years was one year or more ahead of their chronological age were separated, both their parents were found to have significantly higher height and weight than the corresponding averages for

of testes, pubic hair and voice changes than between chronological age and *the same characteristics* There was also a tendency to a greater correlation between skeletal age and development of breast, penis and moustache than between chronological age and the same characteristics, but no significant differences have been shown.

The skeletal development was also compared with different social conditions. The skeletal development of children where the parental occupation was manual work was significantly *more retarded than that of* children of the professional classes. No significant retardation could be shown in children from families where the assessed income was below 20 000 Danish kroner a year Whether or not the mother was employed outside the home appeared to have no effect on the skeletal development of the children But the skeletal development of children from overpopulated dwellings was retarded compared to that of children *with more adequate housing* This finding only applies to children from families where the fathers were manual workers.

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51 Growth of Swedish Children up to 7 Years of Age

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From a longitudinal study of growth and development of children started in Stockholm in 1955 data of body growth are presented from birth to 7 years of age

The material consists of 212 children, 122 boys and 90 girls. The children have been measured at regular intervals, 7 times in the first two years and thereafter once a year on birth date This longitudinal procedure has given not only norms for different age groups but also for the rate of growth between ages.

The body parameters measured are weight height sitting height, biacromial and pelvic width bicondyle width of humerus and femur circumference of head thorax, upper arm and calf and subcutaneous tissue in four different locations.

Means for the different distance and

Thus growth hormone levels seem to be lower in infants of diabetic mothers than in normal infants, the rise in growth hormone levels after insulin-induced hypoglycemia being less marked.

This difference seems to be more marked at the age of 5—6 days than during the first 24 hrs. Even hyperglycemia induces a rise in growth hormone levels in infants of diabetic mothers, as it does in normal infants.

TABLE 1 *Data about the infants.*

	No	Birth weight	Gestation time
Normal infants	10	2.560—3.910g	38—41 weeks
Infants of diabetic mothers	5	2.370—3.800g	36—38 weeks

TABLE 2. *Growth hormone and blood glucose levels during intravenous insulin load.*

	Normal infants		Infants of diabetic mothers	
Age	5—24 hr	5—6 days	5—24 hr	5—6 days
GH-levels prior to insulin	70— 90 mμg/ml	27— 60 mμg/ml	45— 52 mμg/ml	22—37 mμg/ml
GH-levels 45 min. after insulin inject.	110—190 mμg/ml	50—110 mμg/ml	55—110 mμg/ml	32—65 mμg/ml
Blood glucose prior to insulin	38— 64 mg/%	45— 96 mg%	3— [illegible] mg%	38—35 mg%
Blood glucose 45 min. after insulin injection	5—40 mg%	22— 53 mg%	0— 15 mg%	2—20 mg%

4 IE of insulin/m² body area was given intravenously. The sample 45 min. after insulin injection in all patients showed the top values. The following samples showed rapid fall in GH-levels.

the parents of all the children The parents of children with slower than average maturation did not, however differ in their height and weight from the average levels.

Morbidity in the material was caused mainly by infections These did not have any demonstrable effect on bone maturation. Height and skeletal age were clearly correlated both boys and girls of higher than average height also had a significantly higher skeletal age than children of below average height.

It is emphasized that national, genetical environmental and individual variations in skeletal maturation must be accounted for when skeletal age is used in assessment of the influence of specific pathological factors, e.g chronic diseases on the development of children

53 Growth Hormone Levels during the First Week of Age in Normal Infants and Infants of Diabetic Mothers

O WESTPHAL

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Growth hormone levels during intravenous glucose load have been studied by radioimmunoassay of normal newborn infants and infants of diabetic mothers.

Radioimmunoassay was carried out by minor modifications of the procedure described by Roth *et al* Blood glucose was measured with a glucose oxidase method the protein being precipitated with $Zn(OH_2)$

On 10 normal infants, delivered by Cesarean section, intravenous insulin loads with 4 IE insulin/m² body area were performed between 5—24 hrs of age and again on the same patients at the age of 5—6 days. For the study a small polyeten tube was placed in the umbilical vein. Blood samples were collected every 15 minutes until 105 minutes after the insulin injection

The same investigation was carried out on 5 infants of diabetic mothers, delivered by Cesarean section. The data on the infants are given in table 1 and the results in table 2

The infants of diabetic mothers furthermore got an intravenous injection of 0.5 g glucose/kg body weight 70 minutes after the insulin injection. 30 minutes after the glucose injection a slight second rise in growth hormone levels was registered at the age of 5—24 hrs as well as at the age of 5—6 days. This unexpected rise of hyperglycemia, earlier shown by Cornblath *et al* has been noted even in normal infants in the same age groups

appear early. Dental development measured in this way is advanced but to a much less degree than skeletal development. The results obtained are to be regarded as preliminary but may suggest that dental development is less influenced by the androgens produced by the adrenal cortex than skeletal development.

55 Circulatory and Respiratory Dimensions in Relation to Growth Differences

B. ERIKSSON

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The question of how a child grows with regard to height and weight has been studied by many authors. Many investigations have been made of children with differences in height — that means short and tall children — and how they differ from normal children of the same chronological age.

The development of circulatory and respiratory dimensions during growth has also been studied. We know how the heart volume changes during growth and it has been demonstrated that the best correlation is to the body surface. Lung volumes also follow the growth curve, the best correlation being to the cube of the height. The total amount of haemoglobin also changes when the child grows, the best correlation being to weight. These circulatory and respiratory dimensions also determine the functional capacity. The problem of why these circulatory and respiratory dimensions follow these parameters has been discussed. The problem of how the appearance of short and tall children is related to their circulatory and respiratory dimensions has been the aim of a pilot study. It was demonstrated in the study that some of these dimensions seemed to be abnormal in relation to the height, weight, or body surface. Thus although the vital capacity of short children seemed to be supernormal in relation to their height, their heart volume seemed to be almost normal in relation to their body surface. The total amount of haemoglobin seemed to be somewhat variable and the functional capacity seemed to be less than the normal for their age and sex. It seems to be of great interest to see whether these circulatory and respiratory dimensions follow chronological age or biological maturity. Further investigation seems to be necessary.

SESSION VI

CHAIRMAN Bo Vahlquist Uppsala

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54 Dental Development in Congenital Adrenal Hyperplasia

C. G BERGSTRAND and R. FILIPSSON

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The usual way of evaluating the degree of physical maturation in growing individuals is by estimation of the skeletal development. It could perhaps be assumed that determination of the dental development would be a valuable complement especially as it is easy to perform. It has, however been found that in normal children the number of erupted permanent teeth at a certain age is not too well correlated to other indicators of physical maturation

On the other hand it has been demonstrated that in certain endocrine disorders dental development is definitely retarded and it was therefore thought of interest to study the dental development in a number of children with the adrenogenital syndrome where premature eruption of the teeth seemed likely The total material included 13 boys and 9 girls of whom 6 boys and 2 girls had been adequately treated with cortisone The rest had been inadequately treated or had received no treatment at all When the inadequately treated group was compared with a control group of normal children it was found that the dental age of the children with adrenogenital syndrome was rather evenly distributed around the normal average In a few cases it was possible to estimate the root development of the teeth radiographically this development being normally well correlated with skeletal age

Root development in these cases was advanced but to a much less degree than skeletal age A third method developed by Filipsson, was also used. The age at which minimal rate of dental eruption occurs is correlated to the degree of physical maturation In children demonstrating early maturation (e.g early menarche in girls) minimal rate of dental eruption occurs at an earlier age than in those who mature later In the children with adrenogenital syndrome minimal rate of dental eruption tends to

appear early Dental development measured in this way is advanced but to a much less degree than skeletal development. The results obtained are to be regarded as preliminary but may suggest that dental development is less influenced by the androgens produced by the adrenal cortex than skeletal development.

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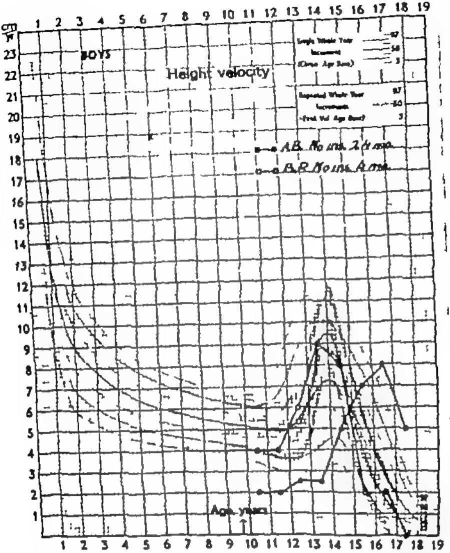

Fig. 1

During the years 1957—59 a number of diabetics who had received initial insulin treatment were given sulfonylurea drugs alone during their remission phase. They were not allowed to have glycosuria or acetonuria, or any clinical symptoms without reinstitution of insulin. Our clinical impression was that they had a somewhat reduced capacity to put on fat, in agreement with our present knowledge of lipogenesis as the most sensible indication of insulin action. The growth pattern of these children indicates that the presumed endogenous insulin release was insufficient

56 Growth Pattern in Juvenile Diabetes

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In a previous study (1) it was observed that juvenile diabetics of at least 15 years duration were somewhat shorter than normal. The reduction in height was most pronounced for men of whom 13% fell below —3 S.D

In a material of about 150 diabetic school children and non-diabetic social twins the difference in height was much more pronounced before puberty than after (2) When this material was investigated after another 5 years the same tendency was seen As previously found, diabetic girls weighed more than their non-diabetic controls after puberty but diabetic boys less in all age groups. Age at menarche was about 6 months later in diabetics.

In this follow up study those who had reached full stature were compared No diabetics fell below — 2 S D *but in the matched pairs diabetic* boys were still significantly shorter Age at onset of diabetes was without influence Skinfold thickness measured with a caliper over three sites was greater in diabetic girls and boys of all ages. When weight for a given height was expressed as S.D from the mean in a normal material the diabetics showed somewhat higher values than non-diabetics. The findings indicate a reduced muscular mass in diabetic boys and pronounced increase of body fat in diabetic girls.

All parents of subjects who had reached full stature were asked by letter to report their actual height. Parent-child correlations in height were calculated as well as midparent child data as used by Garn, Rohman (3) in other studies The figures (Table 1) for diabetics are lower in all age groups but one, indicating a disturbed growth

However at onset most diabetic boys have a slight increase in height *in comparison with normals* In the following years there is a tendency to a lowered growth velocity but a catch up growth then seems to take place.

TABLE 1

		No. of subjects	Subject's height	Father's height	Mother's height	Father child	Mother child	Mid-parent child
Boys	Diabetics	34	176.2	177.2	161 4	0.40	0 47	0.60
	Non-diabetics	21	179 4	176.5	164 2	0.50	0.68	0 72
Girls	Diabetics	28	164.9	178.4	163 9	0.48	0.36	0.50
	Non-diabetics	28	166.7	1 6.1	164.0	0.48	0 62	0 71

Mean values for parents height and parent-child correlation in diabetic and non-diabetic children, who have reached full stature.

58 Skeletal Age of Children with Congenital Heart Disease

W RYBA, G. HEDVALL, L. E. CARLGREN

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The skeletal age of 104 children with congenital heart disease was estimated according to the method of Tanner and Whitehouse (already described in these papers) and a new method from the Karolinska Hospital in Stockholm (Eklöf and Ringertz) The latter authors measure the length and width of some bones of the wrist, using ten parameters. Their normal material has been 1000 children, 1—15 years of age These two methods were found to give roughly equal results, and the tables presented give the values according to Tanner and Whitehouse

The patients were divided into three groups those with stenosis (33) with left-to-right shunts (51) and those with cyanotic vitia and reduced pulmonary blood flow (20) Most children with combined vitia could be put into one of these groups. A few children who had already been operated upon were included, and children with very different severity of vitium e.g small VSD without clinical significance, and major VSD with pulmonary hypertension. Children less than one year old were excluded, also those with complicating malformations or embryopathia, and those few with rare forms of vitia which could not be included in these three groups. These children were found to be slightly underweight, at least when under 7 years of age, whereas their length did not differ from the normal age groups.

As to the skeletal age no significant difference was found between these small groups, and the results are presented in a joint table. A few children can be considered to be definitely late in their skeletal age, and the group of smaller children, 1—7 years old, tends to have a lower mean value for their skeletal age than that normal for their age. The older children are normal in their distribution.

The natural selection of the patients can perhaps account for this children with severe congenital heart disease come to the clinic earlier and those with a murmur as the only manifestation come later perhaps not until school age.

The children with retarded skeletal age tend to be also small of stature for their age.

This investigation has thus shown that children with congenital heart disease are often later in their skeletal maturation than are normal children of the same age. We plan to look at a greater material of children in order perhaps, to discover something concerning the reasons for this.

for normal height velocity An example of a useful way of plotting data is given in Fig 1, where two boys who developed diabetes at the same age and have similar correlations to parents height are compared with the data of Tanner *et al* (4) Of course other factors are involved and no definite conclusions about etiology or pathogenesis can be drawn So far it has also been impossible in any of the materials to find any influence of diabetic treatment on growth

Undisturbed somatic development is however one of the primary goals in the treatment of diabetes in childhood and adolescence. In spite of definite improvements the above data may imply that this generally accepted goal has not yet been reached.

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57 Physical Development of Children with Congenital Heart Disease

P SUONINEN

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The physical developmental pattern of children with different forms of congenital heart disease was studied before and after cardiac surgery The height and weight of the children was correlated with the nature and severity of the heart disease, physical capacity electrocardiogram and hematological data The height and weight of normal Finnish children were used as controls. The collected data were analysed by means of a computer

The present series comprised 91 children with tetralogy of Fallot. There were 56 boys and 35 girls. Nine children received corrective surgery a shunt operation was performed in the remainder of the cases. The mean age at operation was 8.5 years

The height and weight of the boys differed more from the normal values than the corresponding values for the girls both before and after surgery The weight of boys and girls was usually more retarded than the height Children operated upon when 7—10 years old showed the best postoperative improvement. There was a correlation between the hemoglobin value and the physical capacity before and after the operation

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P SUONINEN

Children s Hospital, University of Helsinki

The physical developmental pattern of children with different forms of congenital heart disease was studied before and after cardiac surgery The height and weight of the children was correlated with the nature and severity of the heart disease, physical capacity electrocardiogram and hematological data. The height and weight of normal Finnish children were used as controls. The collected data were analysed by means of a computer

The present series comprised 91 children with tetralogy of Fallot There were 56 boys and 35 girls. Nine children received corrective surgery a shunt operation was performed in the remainder of the cases. The mean age at operation was 8.5 years.

The height and weight of the boys differed more from the normal values than the corresponding values for the girls both before and after surgery The weight of boys and girls was usually more retarded than the height Children operated upon when 7—10 years old showed the best postoperative improvement There was a correlation between the hemoglobin value and the physical capacity before and after the operation

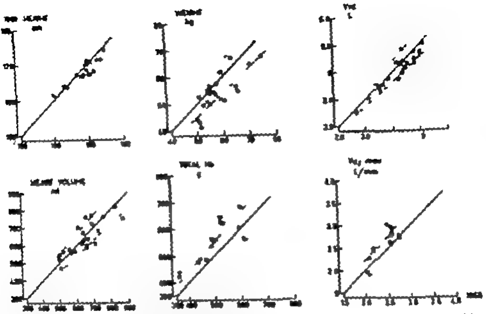

Fig. 1 Individual values for height, weight, vital capacity heart volume, total hemoglobin and maximal oxygen uptake 1963 compared with the values from 1961 Line of identity and lines corresponding to 10% deviation are drawn.
Symbols ○ no longer in training x still in training.

city large even when related to body size — the advanced functional development — was on the other hand the effect of prolonged intense training

REFERENCES

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60 Neonatal Symptomatic Hypoglycemia

Some results from a follow-up study

O. EEG-OLOFSSON, J. GENTZ, U. JODAL, L. R. NILSSON and R. ZETTERSTRÖM

Department of Pediatrics, University of Gothenburg and Department of Pediatrics, Kronprinsessan Lovisas Barnsjukhus, Stockholm

Neither the etiology nor the prognosis of neonatal symptomatic hypoglycemia is sufficiently known. Many of these children, however, are small for dates. Could the abnormal carbohydrate metabolism manifest during the neonatal period be due to metabolic imprinting? Will this be reflected in further attacks of hypoglycemia or retarded somatic growth? Many

59 Influence of Physical Training on Growth? A Study on Girl Swimmers

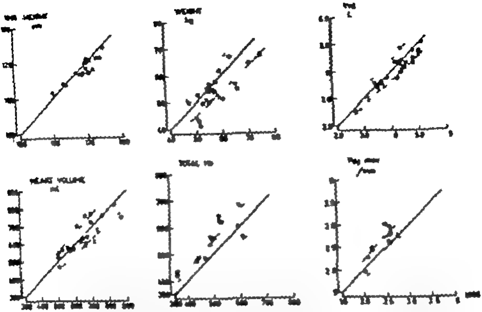
B. ERIKSSON, C. THORÉN, I. ENGSTRÖM and P. KARLBERG

Department of Pediatrics, Karolinska Sjukhuset, Stockholm

In 1961 30 girl swimmers in hard training were examined at the age of 12—16 years. The girls showed a very high functional capacity which was strongly correlated to their large functional dimensions — heart volume, total hemoglobin and vital capacity. Intensive physical training during the period of accelerating growth might explain in several cases why these larger dimensions were obtained.

The girls were also found to be significantly taller as a group compared with untrained normal girls of the same ages. The girls were already significantly taller at the age of seven but the deviation had further increased at the time of examination. This increase in deviation was significant. One probable factor which might explain this increased height is the intensive physical training, as it is well known that physical activity stimulates production of growth hormone. To find out what happened to their dimensions and height after they were fully grown the girls were reexamined four years later. Only four out of the 30 were still active swimmers. The height of all the girls was still significantly higher than the normal, but the deviation had decreased so in relation to the standard deviation it was the same as that at the age of seven. Their functional dimensions had decreased. The total hemoglobin was now within $\pm$ 2 SD. The heart volume had also decreased but was in some cases still over two SD. The vital capacity was unchanged but the value in relation to height was around the mean value ($\pm$ 1 SD). As a result of the decrease of the functional dimensions the functional capacity measured as the maximal oxygen uptake, had also decreased and was now within normal ranges.

The results show that intense training during a period of accelerating growth leads to large functional dimensions and capacity. They decrease almost into normal ranges ($\pm$ 2 SD) after training is broken off. The study has not proved that intensive physical training is capable of stimulating the growth rate. The most probable explanation of the increased height found in the study of girl swimmers seems to be a body constitution characterized by a fast growth pattern in which an early menarche potentiates the height deviation at the age of the first investigation. This would also seem to be a prerequisite for the maintenance of intense swimming training during a period of two to three years and for the achievement of good swimming results on which principles the girls were selected for the study. The huge functional dimensions and capa



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SCIENTIFIC EXHIBITIONS

intriguing questions remain to be answered

14 children from Gothenburg and 10 from Stockholm have been reexamined at the ages of 4—6 years and 8 months — 3 years respectively. Only 5 of the 24 are girls. All had a normal delivery with clinical manifestations of convulsions, apnea or cyanosis starting between 12—72 hours and persisting no longer than one week. All had a blood glucose value below 20 mg/100 ml.

At birth 14 of the 24 children fell below the 10th percentile for weight in relation to gestational age. 5 were in the 10—90 range but rather thin in relation to height. The remaining 5 including 3 of the 5 girls, were above the 90th percentile. None of the mothers have shown any signs of diabetes.

The follow up has included history of convulsions and hypoglycemia after the neonatal period, neurological evaluation electroencephalogram echoencephalogram, psychological testing, intravenous glucose tolerance test, height and weight measurements. The Gothenburg children have also been examined for ophtalmological defects, subcutaneous fat and skeletal age by the Tanner — Whitehouse method.

Among the 24 children 12 have had convulsions and 5 verified hypoglycemia. 13 show pathological electroencephalogram with paroxysmal activity and 6 abnormal neurological signs. 3 have squints and 2 of these defective vision with pale fundi. No cataracts have been noted. 10 have developmental quotients below 85 (Terman — Merill). The prognosis does not seem to be different among those with relapses of hypoglycemia, neither has any difference been detected between children with different weight at birth. However 3 of the 5 girls are heavily retarded, with developmental quotients below 50.

The somatic development is retarded (height, weight and skeletal age) among the children small at birth. This is in accordance with findings by Hepner (1963). No difference has been found in amount of subcutaneous fat.

Neonatal symptomatic hypoglycemia is not a uniform disease, though intrauterine growth often is retarded. The prognosis is grave and perhaps even worse among girls. We have not been able to find a parameter suitable for prognostic judgement in the individual case.

SCIENTIFIC EXHIBITIONS

1 Children's Nutrition Unit, a SIDA Project in the Field of Health Research

G. ALMGÅRD, K. B. BJÖRNESJÖ, Y. HOFVANDER, K. JACOBSSON
K. E. KNUTSSON, O. MELLANDER, T. MELLBIN, RUTH SELINUS
B. VAHLQUIST and G. ÅGREN

Addis Ababa, Uppsala, Gothenburg

The planning of the Children's Nutrition Unit (CNU) which is financed by the Swedish International Development Authority (SIDA) in cooperation with the Imperial Ethiopian Government, started in 1961. The work in Ethiopia began in September 1962. The aim of the project is to elucidate the frequency and character of malnutrition in Ethiopian children, to test an enrichment program with special emphasis on locally available indigenous foodstuffs, and to collaborate in the planning of nutrition programs on different levels.

For the time being seven Swedish experts, four Ethiopian counterparts, and a large staff of Ethiopian technicians are involved. There is a close cooperation between the CNU activities in Ethiopia and four Swedish university institutions, biochemical, pediatric and agricultural (in Gothenburg and Uppsala). Senior representatives of these institutions are members of a special Scientific Steering Committee.

A well-equipped base laboratory has been built in Addis Ababa and is used for biochemical and food analyses. Five field stations have been established in widely different parts of the country and it is estimated that the living conditions and the food habits in these test areas are representative of more than half of the population of Ethiopia (about 22 million). In Addis Ababa a Children's Home is connected to the Unit, where the children are living under controlled conditions with frequent medical examinations. The values obtained from this "control group" will be compared with the findings from the field stations. Different food supplementary mixtures are first tested there for acceptability.

The total number of children included in the baseline studies amounts to 2830. So far about 3600 blood samples have been taken and in addition a large number of stool and urine specimens. Careful nutrition surveys on selected groups of families

discovered and regarded as caused by prematurity and the girl was given the customary treatment. At the age of 2 /₂ years she developed severe anemia, and parenteral vitamin B_{12} treatment was initiated by the local doctor as her brother was known to have anemia responsive to parenteral vitamin B_{12} treatment.

The patient was admitted at the age of 8 years to Turku University Children Clinic. A macrocytic, megaloblastic anemia and proteinuria were diagnosed. The findings are given in detail in Table 1

It is remarkable that this patient had multiple congenital organ anomalies, namely hare lip in addition to kidney impression.

The jejunal juice used in the experiments was obtained by Miller Abbott tube from healthy serviceman, admitted to a military hospital for slight respiratory tract infection.

CASE 2 M.H. ♂

Brother of case 1 At the age of 1 / years macrocytic anemia and proteinuria were diagnosed for the first time. The patient was admitted to Turku University Children Clinic several times and treated with blood transfusions, iron, liver and folic acid. In spite of the treatment he was intermittently anemic until regular parenteral vitamin B_{12} therapy was commenced. During the summertime the patient was well without treatment, but in winter he needed monthly parenteral vitamin B_{12} injection. At the age of 15 he was admitted to the Turku University Children Clinic for thorough examination. A parenteral vitamin B_{12} injection was given two weeks before the admission so the patient was not anemic when entering the hospital, but the blood picture was macrocytic. A persistent proteinuria was diagnosed in spite of vitamin B_{12} treatment. The results are given in Table 1

The healthy person s jejunal juice used in this experiment was obtained by the same technique as in case 1 but from another military hospital patient, admitted for vegetative symptoms.

It has been suggested that a prerequisite for a normal vitamin B_{12} absorption is the existence of a hypothetic releasing factor in the small intestine. It has been claimed that this factor splits the big vitamin B_{12}-intrinsic factor complex, thus allowing the vitamin B_{12} molecule to be absorbed. It has been proposed that the disturbance in the absorption of vitamin B_{12} in this syndrome is due to the lack of this hypothetic releasing factor (Hippe 1966) The conclusions which may be drawn from the cases described here suggest rather the lack or functional disturbance of a specific receptor system in the ileal wall than the lack of releasing factor This assumption is based on the fact that a healthy volunteer s jejunal juice could not correct the defective vitamin B_{12} absorption.

have also been performed and the preparation and consumption of all dishes have been studied

In the exhibit the organization of the project the different field stations, and some preliminary results of initial cross-sectional studies are presented They include the following parameters Body height and weight in relation to age, weight in relation to height head circumference in relation to height, micro-sedimentation rate hemoglobin gammaglobulin immunoglobulins and cholesterol. To illustrate the food situation, consumption data are given from two of the field stations, where the food habits differ widely

Finally, the sero-immune patterns for a number of diseases have been investigated in order to get information on previous illnesses and present immunity situation In the exhibit the incidences of antibodies to Poliomyelitis, Measles Toxoplasma, and the AST are presented as examples of this investigation, which also includes the sero-immune patterns for Pertussis, Salmonella, Typhus fever Q fever Rickettsial pox, Schistosoma, and Syphilis.

2 Selective Malabsorption of Vitamin B_{12} with Proteinuria in Children

R. ANTTILA and H. A. SALMI

Children's Hospital and Department of Physiology University of Turku

A rare congenital familiar syndrome with clinically benign proteinuria and megaloblastic anemia due to selective malabsorption of vitamin B_{12} is known in literature as Imerslund Gräsbeck anemia

In many cases roentgenologically verifiable kidney anomalies accompany the disease. The disturbance in the absorption of vitamin B_{12} is not due to the lack of intrinsic factor but a specific inability of the small intestine to absorb vitamin B_{12}. The detailed mechanism of this defect is unknown In the literature this syndrome is called Imerslund-Gräsbeck anemia, because it was first described independently of each other in 1960 by Imerslund (1) and Gräsbeck et al (3) Altogether 23 cases of this syndrome are published in the literature The aim of this paper is to report two new cases, a brother and a sister with the clinical picture of the same syndrome.

CASE 1 P.H. ♀

The patient was born premature, birth weight 2440 grams. She was operated on for a congenital cleft lip in Helsinki University Children's Clinic and Red Cross Hospital for Plastic Surgery Slight anemia was

3 Immunoglobulin Levels in Premature Infants

T BERG S GUNNAR and O JOHANSSON

Department of Pediatrics and Blood Center University Hospital, Uppsala

Material In 47 infants with a birth-weight less than 2500 g who have been nursed at the department of pediatrics in Uppsala during the period May 1966 up to April 1967 repeated determinations of the serum concentrations of IgG IgM IgA and IgD have been made. Owing to the longer period of nursing the smallest premature infants could be followed up for longer periods than the bigger ones. In some cases determinations of the different immunoglobulin levels could be made even after the discharge from the hospital. The infants who have been subjected to exchange transfusions were subsequently excluded. Children with severe infections, for instance septicaemia, have not been included. The material has been divided into 3 groups according to the birth weight less than 1800 1800—2200 g 2201—2500 g

Method The concentrations of the different immunoglobulins have been determined by single radial immunodiffusion in agar gel according to Mancini et al. (Immuno-chemistry 2 235, 1965) This method is simple to perform, has a good precision and a fairly high sensitivity the lower limit of detection being about 1 mg/100 ml

Results

IgG While the premature infants in the two higher weight-classes do not differ from each other remarkably as regards the IgG-levels during the first weeks of life the group of children with a birth weight of under 1800 g shows a definitely lower IgG-level from the very beginning The smallest premature infants show particularly low IgG-levels, an infant with a birth weight of 1070 g had for instance an IgG-concentration of 1?0 mg* at the age of 6 weeks. The initial IgG-level seems to have a better correlation to the gestational age than to the birth-weight. Similar results have recently been presented in a preliminary report elsewhere. (Lancet I 757 1967)

IgM IgM could be demonstrated in all examined premature infants during the first 24 hours of life with an average serum concentration of 7.8 mg/100 ml. In full term babies we have previously found an average IgM-concentration of 7 7 mg/100 ml in umbilical cord serum. A strikingly rapid rise of IgM levels during the very first days of life is found in practically all infants. Although the bigger premature infants reach, on the average somewhat higher IgM levels it is obvious that in all three weight groups there exists a good ability to synthetize IgM at a very early stage. At the age of 2—3 weeks the children of the lowest weight-class show an average IgM level of 30 4 mg/100 ml. The infants in the intermediary

Examination	Case 1 P H ♀ 8 years	Case 2 M. H ♂ 14 years
Blood picture	Hb 5 1 RBC 1 3 MHb 39 WBC 5200 MCV 116 Av.diameter of RBC 7.9	Hb 11.3 RBC 3 4 MHb 36 WBC 4700 MCV 112 Av diameter of RBC 8.0
Bone marrow	Megaloblastic	Megaloblastic
Serum B^{12}	35 pg/ml (lowered)	60 pg/ml (lowered)
B^{12} binding capacity	Normal	Normal
folic acid	14 ng/ml (normal)	4 0 ng/ml (low normal)
iron	100 μg%	95 μg%
Schilling	0 %	0.2 %
Schilling with IF	0	0 1 %
Gastric juice analysis	Free HCl and IF	Free HCl and IF
General absorption tests	Vitamin A loading normal Xylose loading normal	Vitamin A loading normal Xylose loading slightly lowered
Feces analysis	Normal, no fish tape worm ova, no abnormal flora	Normal, no fish tapeworm ova, no abnormal flora
Urine analysis	Persistent proteinuria 0 5–1 0 ‰ Normal sediment	Persistent proteinuria < 0.5 ‰ Normal sediment Electrophoresis of urine proteins mainly albumin, α^2 and β^1-globulin
Kidney function	Phenolsulphonthalein excretion test 75 % Spec. weight 1016 Ser creatinine 0 4	Phenolsulphonthalein excretion test 80 % Spec. weight 1027 Ser creatinine 0.8
Orthostatic proteinuria	None	None
I V urography	Abnormal impression in renal parenchyma	Normal
Schilling test with normal individual's jejunal juice	0 %	0.3
Treatment with parenteral vitamin B^{12}	Reticulocytosis to 5 % (transfusions given)	Reticulocytosis to 3 (earlier when anemic to 18)

patient during the iontophoresis. It is also essential for the apparatus to give a sufficient strength of current even if the resistance of the skin is high. In order to obtain a satisfactory strength of current (we used 6 mA) it was found necessary to use a battery of sufficient voltage (45 V) and capacity. The patient electrodes were connected via a high resistance rheostat which gave a stable strength of current despite varying electric resistance of the patient. The apparatus that we used was constructed by Mr Agne Nilsson, engineer at the Department of Clinical Physiology.

Results. We found that 6 mA for 8 minutes in general gave satisfactory amounts of sweat. On the average we obtained 132 mg (28—312) of sweat by a single electrophoresis. There was no difference worth mentioning between different skin areas with regard to either sweat amounts or sweat electrolyte concentrations. Burns never occurred with the method used.

5 Infant Health Visitors as Collectors of Statistical Material. Five Typical Research Programs

T BIERING-SORENSEN

The Municipal Agency of Infant Health Visitors in Copenhagen

Five recent studies from the health visitors agency are demonstrated.

EMOTIONAL AND PSYCHOSOMATIC REACTION IN RELATION TO DIFFERENT ENVIRONMENTAL FACTORS

For some years the health visitors have followed one tenth of the children being supervised up to the age of 5 years, and have registered, among other things, the children's emotional stability and the presence of psychosomatic symptoms. The statistics comprise 1104 children who all have been supervised regularly during the first 3 years.

In 10 tables the influence of the housing conditions is demonstrated as well as the parents' occupation, the mother's age, the numerical position of the child in the family, weight at birth and sex, the mother's work outside the home, the mother — child contact, the principles of up-bringing employed, and whether or not the child was supervised by other persons than the mother.

As expected a distinct relation was found between the housing conditions and the children's physical stability. The psychic adaptation seemed somewhat worse when the mother was very young and in the care of only children. Peculiarly enough there seemed to be less symptoms of psychic instability at the age of 3 years among

weight-class have an average IgM concentration of 33 5 mg/100 ml and those in the highest weight-class 43 6 mg/100 ml. In a previous investigation we have found an average IgM level of 31 8 mg/100 ml in full term infants of 6 weeks Thus there does not seem to exist any essential difference between prematurely born and full term infants as regards their ability to synthesize IgM at an early age.

IgA IgA could not be demonstrated in any premature infant in the course of its first days of life The frequency of children with demonstrable IgA after that increases gradually with rising age and from the age of 4 weeks all infants have demonstrable IgA. At the age of 5—6 weeks the premature infants (all weight-groups) have an average IgA level of 6.1 mg/100 ml We have previously in full-term infants of 6 weeks found an average IgA level of 6 9 mg/100 ml

IgD In the whole material of premature infants IgD could only be demonstrated in one infant, who at an age of 3 months had an IgD concentration of 1 8 mg/100 ml.

4 Pilocarpin Iontophoresis — Practical Aspects

T BERG and L. WRANNE

Department of Pediatrics, University Hospital Uppsala

Determination of sodium and chloride in sweat seems to be the most simple and safe method to establish the diagnosis of cystic fibrosis of the pancreas. Whole body heating to provoke sweating has been found dangerous for patients with this disease. Pilocarpin iontophoresis has been widely used to induce sweating since the method was introduced by Gibson and Cooke in 1959 In our experience, however iontophoresis performed by the standard technique is often followed by small skin burns, even with scar formation There have also been difficulties in getting satisfactory quantities of sweat.

Electrodes In our experiments burns never developed under the positive electrode Many materials were used under the negative electrode. Agar gel containing electrolyte solution was found satisfactory in preventing burns 5 grammes of agar were dissolved under heating in Michaelis buffer Circular plates, 5 cm in diameter were cast and used under the negative electrode

Apparatus The electric resistance of the skin is higher at the beginning of the iontophoresis In order to construct a suitable apparatus it is necessary to take into consideration the variations of skin resistance in the

patient during the iontophoresis. It is also essential for the apparatus to give a sufficient strength of current even if the resistance of the skin is high. In order to obtain a satisfactory strength of current (we used 6 mA) it was found necessary to use a battery of sufficient voltage (45 V) and capacity. The patient electrodes were connected via a high resistance rheostat which gave a stable strength of current despite varying electric resistance of the patient. The apparatus that we used was constructed by Mr Agne Nilsson, engineer at the Department of Clinical Physiology.

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STATE OF TEETH AT THE AGE OF 3 YEARS.

In collaboration with Dental College of Copenhagen" children supervised to the age of 3 years have been examined with regard to the conditions of the teeth, among other things to investigate a possible correlation with the habits of eating

As expected an increase of the frequency of caries was found in cases where the children had oversweetened food, or where the mother was apt to give the children sweets between meals.

SUDDEN UNEXPECTED DEATH OF BABIES.

An examination of the health visitors case records for the last years showed 58 babies who had died during the 2nd—1"th month of life — and where the post mortem diagnosis from the Medico-legal institute was

"SUDDEN UNEXPECTED DEATH

In the material there are 19 girls and 39 boys. The greater number of boys is rather conspicuous, if one excludes the 13 girls and the 12 boys *where post mortem examination* showed signs or suspicion of an acute infectious disease.

Of the remaining 33 children 27 were boys and 6 were girls a find which to a great extent supports the assumption that a hormonal factor contributes to the pathogenesis.

Furthermore it is seen that none of the children have had pure breast feeding at the time of death, and also that the period of suckling on a whole has been considerably shorter than for children generally

6 Age Distribution and Life Span of Foetal Red Blood Cells Present at Birth

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Evaluation of red blood cell life span necessitates a knowledge of the age distribution of the cells. In the normal steady state all age groups of red blood cells are present in equal numbers When the steady state is not present information about the age distribution can be obtained from data of production and destruction of red blood cells. Such data regarding the erythrocytes of the human foetus are not yet available. However the

children of a low birthweight than among those of a normal weight There was no sign of difference between boys and girls

Regarding the mother's employment outside the home there was a distinct tendency towards fewer psychic problems in children of mothers working part time outside the home than for children of mothers staying at home A good mother—child-contact proved to have a beneficial influence while on the other hand a rigorous up-bringing gives a high degree of psychic instability

THE DAILY INCREASE OF WEIGHT OF BABIES DURING THE FIRST 6 MONTHS OF LIFE

As errors have been found in the tables at present used for the babies growth new tables have been worked out, the material exclusively comprising children who have been supervised during the first six months of life The children have been weighed on the visiting nurses verified scales at the age of 1 2 3-4 and 6 months and complete statistical correction has been made in all cases when the day of weighing deviated from the 30 days interval

The table mentioned below which with a good approximation indicates the values for healthy breast fed children as well as the necessary corrections for artificially fed children, may be recommended for use in practice as a mnemonic guide

MORTALITY AND CAUSE OF DEATH during 2nd—12th month of life

The statistical survey comprises all children under the supervision of health visitors in the Municipality of Copenhagen during the years 1940—1962 In all, the material comprises 231 400 children in wedlock and 26 800 born out of wedlock, of which respectively 1722 and 344 died during the 2nd—12th month of life.

Through the whole period the mortality remained almost twice as high among children born to unmarried mothers, although the total mortality fell from about 1½ to 1/3% This high mortality was mainly due to various infectious diseases, whereas there was no real difference of mortality because of congenital malformations

	Average increase of weight for breast-fed children			Correction for children artificially nourished	
	grams per day	grams per week	grams per month	percentage deviation	increase of weight per day
1st month of life	25	175	759	(—25 %)	(20 gr)
2nd month of life	30	210	900	+10*	33 grams
3rd month of life	25	175	750	+25	30 —
4th month of life	20	140	600	+25	24 —
5th & 6th month of life	18	125	550	+15%	21 —

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An examination of the health visitors case records for the last years showed 58 babies who had died during the 2nd—12th month of life — and where the post mortem diagnosis from the Medico-legal institute was

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In the material there are 19 girls and 39 boys. The greater number of boys is rather conspicuous, if one excludes the 13 girls and the 12 boys where post mortem examination showed signs or suspicion of an acute infectious disease.

Of the remaining 33 children 27 were boys and 6 were girls a find which to a great extent supports the assumption that a hormonal factor contributes to the pathogenesis

Furthermore it is seen that none of the children have had pure breast feeding at the time of death and also that the period of suckling on a whole has been considerably shorter than for children generally

6 Age Distribution and Life Span of Foetal Red Blood Cells Present at Birth

L. E. BRATTEBY and B. WADMAN

Department of Paediatrics and Medicine and the Swedish Medical Research Council Unit for Experimental Haematology University Hospital, Uppsala

Evaluation of red blood cell life span necessitates a knowledge of the age distribution of the cells. In the normal steady state all age groups of red blood cells are present in equal numbers. When the steady state is not present information about the age distribution can be obtained from data of production and destruction of red blood cells. Such data regarding the erythrocytes of the human foetus are not yet available. However the

children of a low birthweight than among those of a normal weight There was no sign of difference be tween boys and girls

Regarding the mother's employ ment outside the home there was a distinct tendency towards fewer psy chic problems in children of mothers working part time outside the home than for children of mothers staying at home. A good mother—child-con tact proved to have a beneficial in fluence while on the other hand a rigorous up-bringing gives a high degree of psychic instability

The daily increase of weight of babies during the first 6 months of life

As errors have been found in the tables at present used for the babies growth new tables have been worked out, the material exclusively compris- ing children who have been super vised during the first six months of life. The children have been weighed on the visiting nurses verified scales at the age of 1 2 3-4 and 6 months and complete statistical correction has been made in all cases when the day of weighing deviated from the 30 days interval

The table mentioned below which with a good approximation indicates the values for healthy breast fed children as well as the necessary cor rections for artificially fed children, may be recommended for use in practice as a mnemonic guide

Mortality and cause of death during 2nd—12th month of life.

The statistical survey comprises all children under the supervision of health visitors in the Municipality of Copenhagen during the years 1940—1962 In all the material comprises 231 400 children in wedlock and 26 800 born out of wedlock, of which respectively 1722 and 344 died during the 2nd—12th month of life.

Through the whole period the mortality remained almost twice as high among children born to unmar ried mothers, although the total mor tality fell from about 1½ to 1/3% This high mortality was mainly due to various infectious diseases whereas there was no real difference of mor tality because of congenital malfor mations.

	Average increase of weight for breast-fed children			Correction for children artificially nourished	
	grams per day	grams per week	grams per month	percentag deviation	increase of weight per day
1st month of life	25	175	759	(—25%)	(20 gr)
2nd month of life	30	210	900	+10%	33 grams
3rd month of life	25	175	750	+25	30 —
4th month of life	20	140	600	+25%	24 —
5th & 6th month of life	18	125	5.0	+15%	21 —

STATE OF TEETH AT THE AGE OF 3 YEARS.

In collaboration with Dental College of Copenhagen" children supervised to the age of 3 years have been examined with regard to the conditions of the teeth, among other things to investigate a possible correlation with the habits of eating

As expected an increase of the frequency of caries was found in cases where the children had oversweetened food, or where the mother was apt to give the children sweets between meals.

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7 A Cornelia de Lange's Syndrome I — Like Case with Inherited Chromosome Aberration

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Cornelia de Lange's syndrome I is essentially characterized by low birth weight in spite of delivery at term, retarded growth, psycho-motor retardation, microbrachycephaly bushy eyebrows with synophrys, long curved eye-lashes, short upturned nose with flat bridge, elongated philtrum, carp mouth, low set ears, dysplastic hands with proximally placed thumbs and dysplastic feet with syndactyly of second and third toes.

The etiology of the syndrome is obscure A chromosome aberration

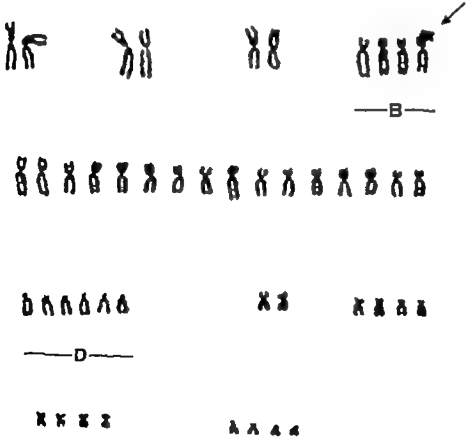

Fig 1 Proband B/D translocation + normal D chromosomes (partial D trisomy).

increase of circulating red cell volume during the last months of foetal life (Fig 1) is an expression of the minimum production i e. the increase of red cell volume equals the production if there is no destruction This estimated minimum production will give rise to a population of red cells, in the newborn infant, with a disproportionate number of young cells (Fig 2) In fact the age distribution is probably even more asymmetrical as the calculated production of red blood cells was underestimated Assuming a mean potential life span of 120 days for cord red blood cells, the uneven age distribution will result in a convex survival curve as shown by a broken line in Fig 3 Cord red blood cells from nine healthy full term infants were labelled *in vitro* with $DF^{32}P$ and transfused into nine haematologically normal adult recipients. The results of these studies are given in Fig 3 The mean life span of these cord red blood cells is apparently considerably less than 120 days. Quantitative calculations of life span distribution are now in progress

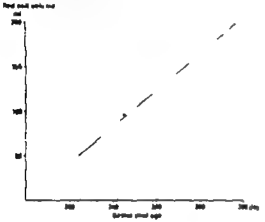

Fig 1 Circulating red cell volume measured by ^{51}Cr technique in newborn infants of different gestational age.

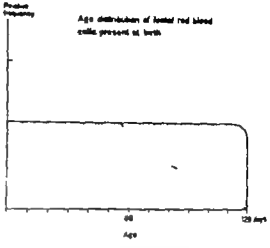

Fig 2 Age distribution of red blood cells in the normal adult (continuous line) — and in the newborn infant (broken line)

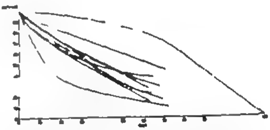

Fig 3 Survival of $DF^{32}P$ labelled cord red blood cells transfused into adult recipients. The broken line shows the expected survival curve assuming a mean potential life span of 120 days.

examined. The proband has only three normal B group chromosomes. Instead of the missing B group chromosome, a chromosome similar in size and morphology to a chromosome no. 3 was found. The D group chromosomes looked normal (Fig 1) The mother and sisters of the proband showed the same picture except for a D group chromosome the long arm of which looked shorter than normal (Fig. 2) The father and the parents and a sister of the mother had normal karyotypes. Hence it is evident that the mother and sisters of the proband have a balanced translocation, a B/D translocation The karyotype of the proband with the normal chromosomes in the D group should thus be regarded as a partial D trisomy

The dermatoglyphs of the proband showed a strikingly lower total ridge count and strikingly higher maximal *atd* angle than those of all her relatives. This fits rather well with the findings in cases of de Lange syndrome reported by Smith (2)

Much argues for this being really a case of Cornelia de Lange's syndrome I but due to the atypical clinical findings mentioned above, we do not consider that a definite diagnosis can be made.

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The dermatoglyphs have been analysed by Dr J M. Berg and Dr G F Smith, Harperbury Hospital, Harper Lane, England

8. Necrotizing Encephalopathy Localized to the Brain Stem in an Infant

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CASE REPORT

The patient presented was a boy the first child of healthy unrelated parents with no known diseases in the family Pregnancy labour delivery and neonatal period were normal. Feeding difficulties and slow development were noted early At the age of 3—4 months the child lost the ability to lift his head in the prone position. He showed no interest in his surroundings and became increasingly irritable. Short tonic fits started. Fever periods occurred without signs of infection.

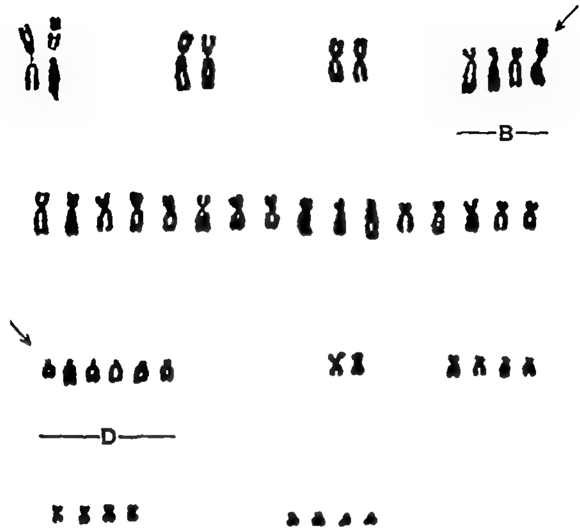

Fig 2. Mother and sisters Balanced karyotype with B/D translocation and deleted II chromosome.

has been discovered in 16 of the approximately 100 cases described in the literature The findings have been described as fragmentation deletion pericentric inversion and transloca tion In spite of normal chromosomes in 20 cases, McArthur and Edwards (1) consider the chromosome aber ration etiology most likely

An eight year-old girl with congeni tal heart disease epilepsy and mental retardation presented an appearance typical of Cornelia de Lange s syn drome I except for normal birth weight normal growth verified by normal ossification age, normally placed thumbs and no carp mouth Detailed clinical and laboratory in vestigations were performed The ap- pearance of the parents and two sis- ters of the girl showed some minor peculiarities. One brother died at the age of two days from multiple mal formations

Chromosomes of the proband and her relatives were studied in blood The modal number of chromosomes was 46 in cultures from all persons

9 Renal Diabetes Insipidus

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Renal diabetes insipidus is a rare hereditary disease characterized by impaired absorption of water in the distal renal tubules, and absence of an increase in renal concentrating ability in response to vasopressin. In the following two affected siblings are presented.

Case 1

Boy S. L., aged 15 months. No information about hereditary disorders in the family parents non consanguineous. The pregnancy delivery and neonatal period uncomplicated. Birth weight 2210 g The child had "always vomited and was frequently constipated Since 6 months of age there were episodes of intermittent fever and profuse sweating. From the age of 7—8 months he displayed signs of motor and mental retardation At admission the boy was hypotonic The skin had a peculiar pasty" consistency The urine was very dilute, the specific gravity varying between 1 002 and 1 015 Serum sodium ranged from 146 to 168 mEq/l (average value 156 mEq/l) Serum chloride level varied between 102 and 132 mEq/l (in average 124 mEq/l) Serum cholesterol on two determinations showed 287 and 350 mg per 100 ml. 200 mU of pitressin given intravenously in the course of one hour failed to produce a urine more concentrated than serum

The patient was given diet low in electrolytes and one tried to give substantial amounts of fluid. This was not always successful, partly because of the patient s refusal to drink, partly because of vomiting A therapeutical trial with Hydrochlorothiazid (Fig 1) significantly lowered the serum sodium and chloride, but the effect was of relatively short duration (some weeks)

The boy has been controlled regularly in the clinic. He is extremely retarded. At 3 years of age he is still unable to walk alone, and he speaks only a few words.

Case 2

Boy J L., aged 5 months. The pregnancy delivery and neonatal period uncomplicated. Birth weight 3600 g. Since 2 months of age episodes of fever At admission his appearance was much like his brother s, and the same "pasty" consistency of the skin was noticed. The specific gravity of the urine varied between 1 004 and 1 010 Serum sodium was 158 mEq/l serum chloride 117—127 mEq/l Serum cholesterol 272 mg per 100 ml The pitressin infusion test was similar to that of his brother

When examined at the age of 7 months he showed no interest in his surroundings and reacted neither to light nor to sound and only slightly to tactile stimulation Pupils reacted sluggishly to light eyegrounds appeared normal The boy was lying in a froglike position he had severe muscular hypotonia and moved very little Reflexes were normal for age Spinal fluid was normal Two earlier electroencephalograms were normal, a third, recorded 3 weeks before his death showed paroxysmal spike activity

His condition deteriorated he became febrile and died at the age of 8 months.

Autopsy findings

On macroscopic examination of the central nervous system abnormalities were seen mainly in the brain stem. A T shaped brownish red lesion was found in the lower part of the mesencephalon and the upper part of the pons under the aqueduct and in the bottom of the fourth ventricle it extended a few mm from the midline on both sides. The posterior columns of the spinal cord were slightly thin and pale particularly in the thoracic region

Histological examination revealed severe demyelinization which besides the lesion seen macroscopically included also the brachium conjunctivum at its decussation and the longitudinal medial fascicle. The findings had the character of astroglial scar tissue with sudanophilic macrophages and marked proliferation of capillary vessels. In addition the superior cerebellar peduncles and the posterior columns of the cervical and thoracic spinal cord were partly demyelinated with only slight gliosis and no capillary proliferation findings characteristic of secondary tract degeneration. Mild gliosis was noted in the optic nerves.

Other autopsy findings were bronchitis, bronchopneumonia, focal pulmonary atelectasis a septic spleen and signs of terminal circularatory failure

Discussion

The clinical picture and the histopathological abnormalities are in agreement with findings previously reported under headings such as chronic Wernicke-encephalopathy or subacute necrotizing encephalomyelopathy About 30 cases are now on record The first case was reported by Leigh in 1951 (2) and the present knowledge was summarized by Lakke *et al* 1967 (1)

A metabolic disorder probably with recessive autosomal inheritance, is assumed to lie behind the condition. Impaired thiamine metabolism and increased production of lactic acid are the two explanations most discussed although neither has been proven

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10 Impedance Pneumography in Newborn Infants

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In 52 healthy fullterm newborns (25 girls and 27 boys) a simultaneous recording of impedance pneumogram (IPG) and EKG was made The apparatus consisted of Impedance Pneumograph preamplifier (E&M) T M C-unit (E&M) and Mingograph 24 (Elema) The ages of the newborns varied from 1 hour to 10 days. From the IPG it was possible to count the frequency of the regular respiration and the change in the impedance (ΔZ) caused by respiration. ΔZ is proportionate to the depth of respiration. The pulse frequency was seen from the EKG The newborns were examined in the supine, prone, right and left lateral and upright positions The IPG was recorded in the anteroposterior (AP Lead) and lateral ('C6-O6R Lead) directions.

It was shown that

— ΔZ (depth of respiration) was maximal both in boys and girls in the prone position in the anteroposterior recordings. Also in the lateral recordings the boys had the highest values in the prone position whereas the girls had the same maximal depth both when lying on the left side and in the prone position.

— correspondingly the frequency of respiration was, on an average, lowest in the prone position, both in boys and girls.

— the regular respiration was often interrupted by short pauses and therefore the frequency was in reality lower than indicated by the frequency of the regular respiration.

— a Cheyne-Stokes-like rhythm was found in 29 newborns.

— the IPG recording was disturbed by cardiogenic changes of impedance in some cases.

Besides this series a simultaneous x ray cinematographic film of the chest and an IPG recording was made on a premature boy (birth weight 2350 gr)

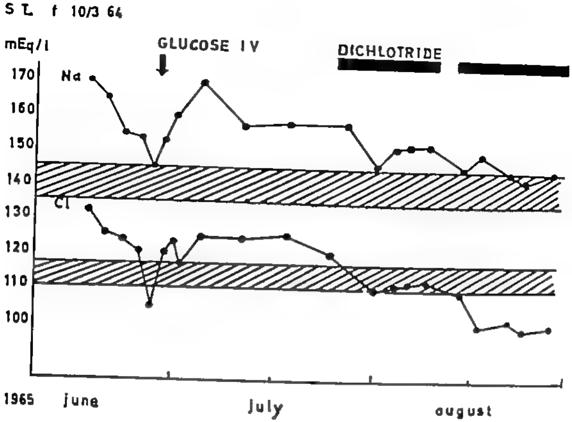

Fig 1 Renal diabetes insipidus. Treatment with Hydrochlorothiazid.

This boy was treated according to the same principles as his brother The results of the therapeutic regime seem to be much more satisfactory than in the first case At two years of age he walked alone and said many words.

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5. Recommended by AB Kabi, Stockholm, Sweden.

12 Acute, Lethal Poisoning after Ingestion of Metallic Lead

N. FORSBY B. FRISTEDT and B. KJELLMAN

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This previously healthy 2 year-old girl was admitted to hospital with vomiting of 10 days duration. She had normal stools, normal temperature and no catarrhal symptoms.

She was pale and lethargic The muscle tone was slightly increased and her neck stiff. She had spontaneous vertical nystagmus and normal optic disks. Haemoglobin was 9 4 gm/100 ml. Stippling of the red cells was noted (299/10 000 counted cells) White cells were 13600/cmm with a normal distribution. Serum electrolytes and glucose were normal There was no albuminuria and urinary sediment was normal. Analyses of cerebrospinal fluid disclosed 0 red cells, 7 white cells 73 mg/100 ml protein and 83 mg/100 ml glucose. EEG showed a slow background activity but no focal abnormalities Inquiries about medicines and poisons were negative The girl died 24 hours after admission.

At postmortem examination a lead button with a diameter of 22 mm was found lying free in the stomach The brain showed oedema with signs of increased intracranial pressure and herniation. There were multiple subependymal petechial haemorrhages in the third ventricle Microscopic examination revealed tiny cortical microinfarcts with disappearance of some neurons and glial proliferation. The parenchymatous organs showed toxic changes. No "dead line" was found in the gingivae. X ray of the femur revealed no deposits in the epiphyses. The following tissue concentrations of lead were found brain 0 69 mg/100 g, liver 5 4 mg/100 g and kidney 3 0 mg/100 g In relation to corresponding figures in the literature these values are extremely high

The button was of a type used as *curtain* weights in the girl's home and still available in the shops. Children can easily swallow them and if arrested in the gastrointestinal canal they can cause severe lead poisoning

11 Methodological Considerations Concerning Blood Glucose Determination in Newborn Infants

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Many methods for the determination of blood glucose concentration are found quite reliable in children and adults. In the neonatal period however special conditions prevail Very low blood glucose concentrations are concerned, and to evaluate the hypoglycemia problem it is necessary to choose methods of glucose determination which are reliable at these low levels

A comparative investigation was performed in which four commonly applied routine methods were used the method of Hagedorn Jensen, based on the reduction power of glucose two modifications of the glucose-oxydase principle and a method based on the colour formation between glucose and orto-toluidin (Hultman) Dextrostix was investigated simultaneously as a screening test

The material consisted of 50 full term, newborn infants and 11 infants of low birth weight. The fasting blood glucose concentration (capillary blood) was determined simultaneously by all methods on the second or third day of life (mean age 46 hrs) Galactose was estimated in all infants to test the reliability of the orto-toluidine method. Only traces of this sugar were demonstrated.

The normal ranges and mean values were estimated The mean values varied from 34—56 mg glucose/100 ml according to the method employed. The method of Hagedorn Jensen (1) yields too high values, because other reducing substances than glucose are present. The glucose-oxydase method with protein precipitation by means of buffered perchloric acid (5) yields too low values, mainly because of the interference of glutathione. — The orto-toluidine method (3 4) and the glucose-oxydase method with precipitation of the proteins by means of NaOH $ZnSO_4$ (2) both yield results which are close to or equivalent to the true glucose concentration Only these two methods are satisfactory with regard to the low blood glucose concentrations from a pediatric point of view

Dextrostix is not reliable as a screening test in the very low blood glucose concentrations in newborn infants.

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13 Favorable Response of Chronic Candidas to Amphotericin B

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A girl aged 9 years had had cutaneous, oral and gastrointestinal lesions since the age of 1 year Most of the nails were also involved (Figure 1) The sputum and stools contained candida albicans No endocrine disturbances were noted

Conventional fungicidal therapy was tried without any improvement. Intravenous amphotericin B resulted in healing of the lesions (Figure 2) Mild relapses have been controlled with intravenous amphotericin B, and lately amphotericin B ointment.

Fig. 1 Hands and feet of a 9-year-old girl with chronic moniliasis before institution of amphotericin B treatment.

Fig. 2. Same patient after the first course of amphotericin B.

14 Death from Asthma in Children and Adolescents in Finland in 1952—65

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Death from asthma is not rare, in spite of the improved therapy. Richards and Patrick in Los Angeles observed in 1965 that death from asthma and admissions to hospital had increased during the previous 20 years.

Data for this study was collected from the archives of the Central Office of Statistics in Finland. All the cases in which asthma was diagnosed were registered. When patients had been in hospital the hospital records were also studied. Cases in which asthma was probably not responsible for the death were excluded. It was not possible to decide if respiratory infections were present, and to what degree. Therefore the present material

comprises all those cases in which in fection seemed to play an important role.

Results

From 1952 to 1961 deaths from asth ma seem to have decreased consider ably (from 6 to 2 cases per year) This may be explained by a decrease in mortality in the age group from 0 to 3 years. In 1961 the mortality rate seems to be at its lowest, and then it increases again (from 2 to 6 cases per year) This latter increase occurs only in the age groups from 3 to 20 years. The decrease in the youngest group is best explained by the improved therapy in respiratory infections, be cause at the same time there also seems to have been a clear decrease in mortality resulting from respiratory infections in this age group It seems impossible to explain completely why the death rate should have increased again in the older groups When the patient reports were studied, we could observe that many of the older pa tients had already suffered from severe asthma for many years. They had often received ACTH or corticoster oids over long periods of time In some cases we considered the possibili ty of an overdose of bronchodilating agents or sympathomimetics. In too many cases patients were brought to the hospital in a moribund state

To get some idea about the develop- ment of morbidity in asthma, our own asthma cases were studied We observed that from 1952 to 1965 there was a large increase of asthma admissions (from 25 to about 50 cases per year) Also there were many more new cases of asthma in 1965 than in 1952 (10 vs 30 cases)

15 Gastric Secretion in Early Childhood

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The gastric secretion of acid and in trinsic factor was studied after stimu lation with 40 microgram histamine diphosphate per Kg body weight in 18 children (aged between 9 and 30 months) without gastrointestinal dis- orders.

As in adults the secretory patterns after stimulation showed a sustained response for acid a wash-out response for intrinsic factor The maximal con centrations of both components were about half of those found in healthy adults.

The stimulated hourly output of acid varied between 0 27 and 3 73 mEq and was related to age body weight and body surface area. The

stimulated hourly output of intrinsic factor varied between 1050 and 3965 units and was also related to age, body-weight, and body surface area.

Acid and intrinsic factor are both products of the parietal cell. The present results indicate a dissociation in the parietal cell function in the first years of life, as the secretion of intrinsic factor is more mature than the secretion of acid.

16 Autoimmunity in Ulcerative Colitis

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In sera from patients with ulcerative colitis an increased incidence of elevated autoantibody titers against colon antigen(s) has been demonstrated. These titer values are not elevated in patients with bacillary or amoebic dysentery, Salmonellosis or ulcerous cancer coli. The autoantibody titers in ulcerative colitis do not correlate with clinical factors such as extent of colon lesions, duration or severity of disease or presence of extracolonic symptoms. Pancoloproctemy does not seem to influence the titer levels. Lymphocytes from patients with ulcerative colitis have cytotoxic effects on foetal human colonic mucosa cells grown in vitro, sera have not. The colon antigen is a mucopolysaccharide related to but immunologically distinct from blood group substance A and H. The autoantibodies are usually found in 19S — immunoglobulin and to a lesser extent in 7S.

The colon antigen from man, rabbits and rats cross-react. Immunization of rats and rabbits with homologous and heterologous colon antigen in Freund's complete adjuvans provoked autoantibodies against colon. The colon antigen cross-reacts with a bacterial antigen from E. coli 0 14. The incidence of elevated autoantibody titers against colon is higher among relatives of patients with ulcerative colitis than in the general population.

Autoimmunity in ulcerative colitis might possibly be provoked by immunization (infection) with a bacterial strain cross-reacting with colon antigen(s) which in predisposed individuals breaks the natural tolerance. This might possibly be of importance in the pathogenesis of the disease.

17 Physical Training for Babies

P J NORDENFELT

Stockholm

Three movements are recommended, each to be practised four or five times every day at two or three of the daily nursing hours. Training may be commenced when the child is two or three weeks old. At this age the child has a high muscular tonus (strength) and can be lifted quite easily by his arms or legs. If training is started later, more care must be exercised in the beginning. The movements should always be performed gently and slowly, while watching the child. The child must take active part in the exercises.

The movements (directions for use)

1) put hands around the child's body supporting his chest with the palms, lift the child into the air
2) put hands around the forearms of the child, thumbs in the firm grip of the child's hands (resting between his finger and thumb), lift the child into the air
3) take a firm grip around the child's ankles, lift him into the air, his head down

This last exercise should be presented with special care so as not to frighten mothers and nurses. The child usually enjoys this exercise best of all.

This training program gives the child not only a well-developed musculature but also an increased confidence, a better ability to get on successfully in unusual situations, and a greater inclination for moving than other children. Young parents usually learn very soon to handle their child with confidence and sureness (without fear or insecurity). The child gains, in addition, an increased feeling of security through the close communication with his parents at training intervals.

For twenty years or so this training program has been recommended and demonstrated to many mothers at my infant care centre in Stockholm and privately. A great number of parents have continued the daily program every day over a long period.

No disadvantages whatsoever have been observed; the parents have been happy and satisfied, and the children showed, quite obviously, greater activity and mobility by the end of their first year than did children who had had no training program.

However encouraging, it is not these results that have led to physical training for babies being presented here now, but the observations made during the last three years at a children's home. This home — Lillgården, Upplands Bro — accommodates 16 children, most of them newborn, transferred directly from the maternity hospital. According to a unanimous report by the staff responsible, this form of physical training has, in a conspicuous way, improved the development of the children.

My colleagues are therefore recommended to introduce the system in all departments, with healthy children.

Physical training of this kind has been practised in several countries in Finland, for instance, it has already been recommended for a considerable period at the infant care centres in Copenhagen and Oslo it was practised for some years during the forties Professor A. Tour and others in Leningrad have for many decades now been advocating systematic physical training for babies.

18 Sound Spectrography in Pediatric Diagnosis

J LIND O WASZ-HÖCKERT G ROSBERG K. THEORELL
E. VALLANE, T PARTANEN and V VUORENKOSKI

The Wenner-Gren Research Laboratory Norrtull Hospital, Stockholm and Department of Pediatrics, University of Oulu

Part I

SPECTROGRAPHIC IDENTIFICATION

44 spontaneous cry signals recorded before the meal from 8 infants with the chromosomal syndrome Maladie du Cri du Chat and 38 pain cry signals obtained after a single pain stimulus (pinching) from 20 infants with Down syndrome and from 8 with Kernikterus and 10 with hyperbilirubinemia have been analyzed with sound spectrographs.[1] It has been demonstrated that these three groups have cries which are specific and different from the normal material

[1] Sona-Graph 661 A, made by Kay Electric Co., N J and Voiceprint, made by Voiceprint Laboratories, Inc Somerville, N J

Part II

AUDITIVE IDENTIFICATION COMPARED WITH SOUND SPECTROGRAPHY

90 pediatricians, general practitioners and medical students were tested as to their ability to recognize the cry response to painful stimulus (pinching) of ten newborns and young infants with asphyxia or brain damage from randomized series of ten normal pain cries. The results indicate that the average number of correct answers was 15 4 out of 20 cry samples. The best identification (90—97 %) of pathological cases was made in 3 perinatally asphyctic, brain damaged cases and in 2 cases with hyperexcitability syndrome. The spectrograms of these cries show also the most evident

difference from cries of normal infants. The cases of hyperbilirubinemia, chromosomal aberration and hydrocephalus have also been well identified (81—89%). Only one of the pathological cries was poorly identified (47% diagnosis meningitis E. coli). The acoustical features of the best and poorest identified pathological and normal cries are shown and compared with normal material.

19 The Smaller of Twins and Hypoglycemia

S. OSEID and O. AAGENÆS

Pediatric Research Institute, University of Oslo, Rikshospitalet

Spontaneous delivery 5 weeks before term because of severe toxemia. Identical twins with birth weights of 2170 g and 1500 g. Both were placed in an incubator for 6 weeks. No convulsive episodes occurred and there was no clinical suspicion of hypoglycemia.

The bigger twin has developed normally but suffers periodically from headaches. An abnormal EEG was found in 1966; there has been no improvement on Fenemal treatment.

The smaller twin has occasionally complained of abdominal pain. 4 years old he was referred to hospital with generalized convulsions and hypoglycemia. A similar attack occurred 6 months later.

There has been a tendency to hypoglycemic episodes during the night and early morning; these have been relieved by food intake.

There are no abnormal findings on physical examination, EEG is normal.

The smaller twin develops hypoglycemia on fasting over 14—16 hours. There is no increase in glucose levels following glucagon administration after a 24 hours fast, while there is a normal response following fasting over night. There is an exaggerated response to insulin with fall in plasma glucose level to 18 mg/100 ml following insulin 0.1 i.u./kg intravenously. The HGH response is normal; there is also an increased excretion of catecholamines following insulin administration. The leucine tolerance test is normal.

All tolerance tests are normal in the bigger twin.

There is no difference in intellectual development, both twins being normal.

The tendency to hypoglycemia in the smaller twin is probably related to intrauterine malnutrition in a twin small for date.

20 Perinatal Mortality in North Finland Correlated to Social and Economic Factors

A Community Study

P RANTAKALLIO

Department of Pediatrics, University of Oulu

This is a community study covering some 12,000 childbirths in North Finland in 1966. The area involved covers about 160 000 sq.km, extending 390 km north and 350 km south of the Arctic Circle The total population is about 660 000 The study is prospective information on participants was collected by questionnaire prior to the delivery and information on the child's fate up to the age of 28 days was obtained in follow-up examinations. Information is available on 97 per cent of the deliveries in this area during 1966 All cases in which the child's birth weight was not less than 600 g were classified as deliveries.

According to the preliminary data available the perinatal mortality in the material is 2 6 per cent, including 1 4 per cent stillbirths. 52 per cent of the perinatal mortality in single births consists of infants with birth weights under 2500 g The perinatal mortality of these infants is 33 per cent. The total frequency of infants with birthweights under 2500 g is 4 1 per cent.

For treatment of the data, separate groups were formed of children who died in the perinatal period, of all twins, and of children with birth weights under 2500 g. 1000 controls were obtained by random sampling from the remainder approximately 11 000 infants, using a computer

The attached table shows perinatal mortality in the different groups in relation to the father's occupation.

Father social class	Control group %	Perinatal deaths all %	Perinatal deaths birth weight under 2500 g %
I	3.3	3.5	3.1
II	13 4	14.3	15 9
III	34.3	31.2	30.5
IV	17 7	20.5	20 1
Farmer area of land under plough 8 hectares or mor	8.8	6.2	5.5
Farmer area of land under plough less than 8 hectares	14.9	14.9	14.6
Unknown	3.6	7 4	10.3
Total	100.0	100.0	100.0

A detailed analysis will be carried out concerning the influence of the different factors on the child's birth weight and perinatal mortality in the present material. The study of the surviving children will also be continued: their growth and development will be followed up and the high risk groups analysed.

21 Follow up Study of 18 Infants with History of Coxsackie B-5 Virus Meningitis during Neonatal Period

P. RANTAKALLIO, A. L. SAUKKONEN, U. KRAUSE
and O. WASZ-HÖCKERT

Department of Pediatrics and Department of Ophthalmology, University of Oulu

The series consists of 18 full term infants who had had Coxsackie B-5 meningitis in their neonatal period in July—September 1966. Fig. 1 gives their dates of birth, ages at onset and periods of hospitalization. Seventeen of the children acquired the infection at Oulu Municipal Maternity Hospi

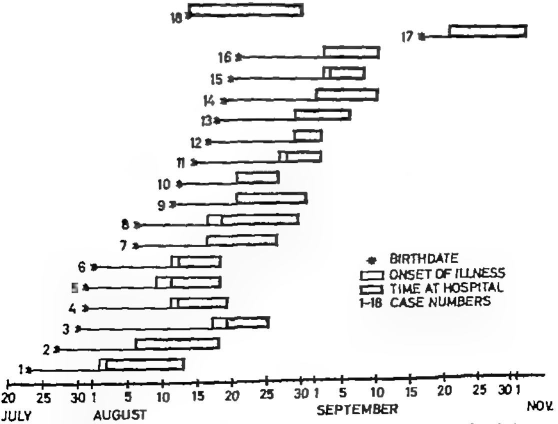

Fig. 1. Children's birthdates, dates of onset of illness, and time spent at hospital.

tal and one (Case 18) at Oulo University Obstetric Clinic. The virological and serological diagnoses were made at the Turku University Institute of Virology Turku, and the State Serum Institute, Helsinki.[1]

The cells in the cerebrospinal fluid of all the cases except one exceeded 100 per cu mm, and in five cases 1 000 per cu mm. Other symptoms common to all cases were fever hyperirritability and anorexia. The symptoms began on approximately the 7th day of life, except in Case 18 where infection had been acquired in utero this infant had been delivered by Caesarean section since the mother had high fever Myocarditis was suspected in the child immediately on birth, and verified later

No instance of subdural effusion was noted in the series.

At follow up examination at the age of 6 months the neurological status and development of all the children was found to be normal. Their weight, height and circumference of head were within the normal limits. Skull and thorax x ray were normal, except for Case 18, the child with myocarditis, whose heart was dilated. The ophthalmologic findings are shown in Fig. 2. Suspected positive findings numbered 7 of the 18, although the causal connection with meningitis was definite only in the suspected optic atrophy The findings will be analysed in greater detail in connection with the follow-up examination at one year

[1] By Kaisa Lapinleimu, Reino Mäntyjärvi and Paula Rantakallio the results will be published separately

Case Number	Findings	Case Number	Findings	Case Number	Findings
1	Divergent squint	7	Convergent squint	13	Normal finding
2	Normal finding	8	Normal finding	14	Normal finding
3	Normal finding	9	Normal finding	15	Megalocornea
4	Meningocele?	10	Normal finding	16	Normal finding
5	Divergent squint?	11	Normal finding	17	Divergent squint
6	Normal finding	12	Optic Atrophy?	18	Normal Finding

Fig. 2 Ocular findings at the age of 6 months

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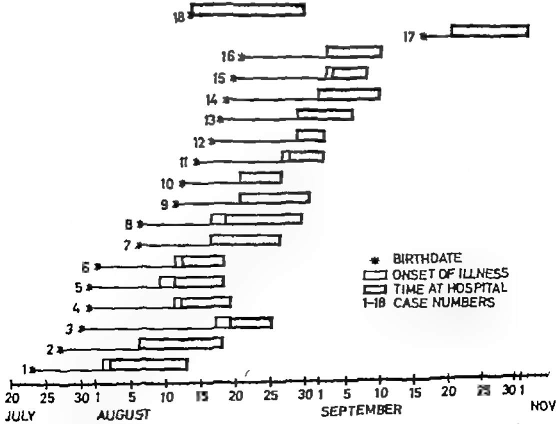

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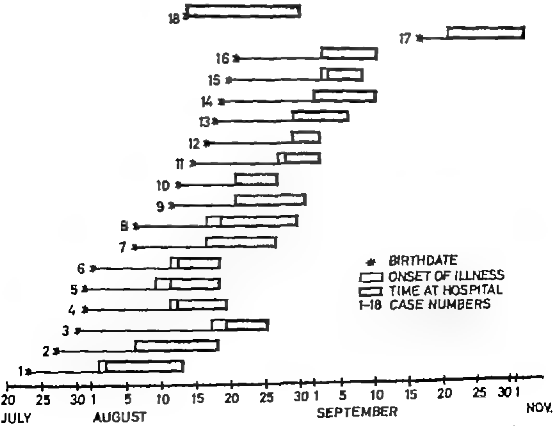

Fig 1 Children's birthdates, dates of onset of illness, and time spent at hospital

is replaced. The prosthesis also makes the feeding easier closing part of the palatal defect. Careful control and adjustment of the prosthesis prevent the formation of pressure sores.

As soon as the orthodontist is satisfied as to the alignment of the dental arch, the child is transferred to the plastic surgery department for operation. The hard palate, the floor of the nostril and the lip are then closed. In the afternoon the child is re-admitted to the pediatric department. The bilateral cases are operated upon in two sessions. Six days after the operation the child is discharged to its home.

At the age of two years, the patient is admitted to the Plastic Surgery Department for closure of the soft palate. In the meantime the child has been under the surveillance of the orthodontist, but no major orthodontic treatment is given until the appearance of permanent teeth.

Children with cleft palate only — group III — are also operated upon at the age of two years, and are of minor interest as far as the orthodontist is concerned.

It is a well known fact that some children with cleft palate are more prone to oto-laryngological disorders than other children. The oto-laryngologist is therefore an important member of the team.

As the child grows older and starts talking the speech therapist comes into the picture to assess possible speech defects and give advice. Speech therapy is started when considered necessary.

At the age of five it must be decided whether the child will need an additional operation to achieve an adequate oro-nasal sphincter mechanism. If this is considered indicated, the child is then admitted for operation. At the same operation minor labial corrections may be carried out.

In the following years the child should be regularly studied and examined by the team. The orthodontic member is usually the most active in this period, guiding the erupting teeth into normal position.

Final correction of the lip and the nose, including submucous resection of the nasal septum, is delayed until the age of 14—15 depending on the physical development of the child.

A retention bridge to maintain the dental arch is not permanently constructed until the age of 18. Then — and only then — can the result of the treatment be finally assessed.

22 Teamwork in the Treatment of Cleft Lips and Palates

H. SCHJELDERUP and S. KVINNSLAND

Department of Plastic and Reconstructive Surgery, Department of Pediatrics, Haukeland sykehus and Orthodontic Department, The Odontologic Institute, University of Bergen

The treatment of children with cleft lips and/or cleft palate is both difficult and time consuming. It covers so many fields of medicine that multilateral teamwork is necessary.

Members of the team being developed in Bergen are the following: plastic surgeon, pediatrician, orthodontist, otolaryngologist, speech therapist and child psychiatrist. It is considered feasible that the plastic surgeon should serve as the coordinating member of the team.

Classification

As demonstrated in the exhibition the following classification is used.

Group I

In these cases only unilateral or bilateral clefts of the lip are present. The alveolar process and the palate are unaffected, with certain exceptions (see group III).

Group II

In these cases the cleft extends from the lip right through the alveolar ridges and the hard and soft palate. There may be an unilateral or bilateral cleft, the latter representing the most difficult problem both surgically and orthodontically.

Group III

In the majority of cases a cleft affects the palate only. There are varying degrees from bifid uvula to a cleft extending the whole way through the palate right to the alveolar process. The cleft is always median.

To complete the picture it should, however, be mentioned that there are a few cases in which there is a combination of group I and group III, i.e. a cleft lip with an intact alveolar process but with a median cleft of the soft and/or hard palate (again the exception confirming the rule).

Group I cases need no preliminary orthodontic treatment and are admitted for operation at the age of about 3 months.

Within a week after birth the child in group II is admitted to the Children's Department and orthodontic treatment is started with the aim of bringing the jaw segments into correct alignment. This is achieved by an orthodontic prosthesis constructed for widening the dental arches while external pressure is applied to the premaxillary segment to bring this into correct position.

It has been questioned whether the prosthesis is troublesome for the child to wear. This does not appear to be so. The children cry when it is removed and quiet down as soon as it

is replaced. The prosthesis also makes the feeding easier closing part of the palatal defect. Careful control and adjustment of the prosthesis prevent the formation of pressure sores.

As soon as the orthodontist is satisfied as to the alignment of the dental arch, the child is transferred to the plastic surgery department for operation. The hard palate, the floor of the nostril and the lip are then closed. In the afternoon the child is re-admitted to the pediatric department. The bilateral cases are operated upon in two sessions. Six days after the operation the child is discharged to its home

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A retention bridge to maintain the dental arch is not permanently constructed until the age of 18. Then — and only then — can the result of the treatment be finally assessed.

23 The Turner Phenotype in Three Brothers with Ichtyosis Vulgaris

S. SIMILA and U KASKI

Department of Pediatrics, Oulu University

Turner s syndrome appears mostly in phenotypic females. Its characteristics were described by Turner short stature webbing of the neck cubitus valgus and sexual infantilism. There are also other somatic anomalies.

The Turner phenotype in the male is far less common Lenz (7) estimates the insidence ratio in men and women at 1 10

The Turner phenotype in man corresponds clinically to Turner s syndrome but exhibits more often mental retardation, ocular deformities, and cardiac anomalies (3) The gonadal development ranges from normal to complete gonadal agenesis (3)

The etiology of Turner s syndrome in the female usual karyotype 45/XO or less frequently sex chromosomal mosaicism or translocation is easily understood from x-chromosomal non disjunction or dissolution The karyotype of the male counterpart is usually normal, 46/XY sometimes with x-chromosomal mosaicism or aberrant x-chromosomes Modern cytogenetic research therefore, cannot explain the etiology of Turner's phenotype in the male merely as a chromosomal aberration

The Turner phenotype may occur familially It has been described in two brothers (1) in a sister and brother (8 9) and in two sisters (2 4 5) The present case involved four brothers, three with a typical Turner phenotype No consanguinity was present in the two preceding generations, and the boys mother had had no miscarriages.

The three brothers showed the following typical stigmas short stature, webbing of neck cubitus valgus, low hairline low set ears, shield like chest, and various other skeletal anomalies. Their karyotype was normal 46/XY The younger two had unilateral kryp-

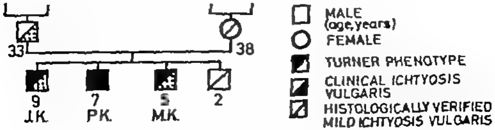

TABLE I PEDIGREE OF THE FAMILY

torchism. The penis, palpable testes, excretion of 17-ketosteroids and gonadotropins were normal and related to age. Mental development was normal, and no renal or vascular anomalies were noted. Mother father and the youngest brother were clinically healthy

The boy of 7 had clinically established and histologically verified ichtyosis vulgaris. The skins of the 9- and 5-year old brothers appeared clinically healthy but mild histological alterations suggestive of ichtyosis vulgaris were traced. The father's skin exhibited similar histological findings, whereas the mother and the youngest son had clinically and histologically normal skins.

The ichtyosis vulgaris of the present family suggests the autosomal dominantly inherited form rather than the sex linked, recessive type. Its dominant inheritance seems irregular and incomplete (6)

The strongly familial Turner phenotype in this family suggests an x chromosomal or autosomal recessive type of inheritance. Unfortunately the irregularly dominant inheritance of ichtyosis vulgaris provides no further clues as to its etiology There may therefore, exist no single etiologic factor responsible for the Turner phenotype in males.

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24 Hyperprolinemia without Renal Disease

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Hyperprolinemia is a rare inborn defect of metabolism. Efron (1) has demonstrated that apparently two types of this disease exist: type I is a defect of proline oxidase enzyme and type II a defect of PC-dehydrogenase. A description is given here of a family with four living children of which two were suffering from hyperprolinemia type II (Fig. 1).

The index case, a boy, was admitted at the age of 6 months; he had had prolonged epileptic seizures. His birth and early development were normal. On admission, the patient was flabby, somnolent and hyperthermic. On the second day an erythematous rash appeared. The seizures subsided within three days under antiepileptic treatment. Few pathological findings were made on laboratory examination, although the EEG was extremely abnormal. Strong prolin, hydroxyprolin and glycinuria were found in biochemical studies. The serum proline concentration was 398 mikrog/ml. After the discovery of this metabolic anomaly the whole family was examined. The oldest child in the family had died at the age of 4½ years, following severe convulsive disorders and progressive mental retardation from the age of 6 months. The parents and other living children were all healthy, although a boy aged 7 had also had a metabolic anomaly similar to the index case. His serum proline concentration was 334 mikrog/ml. The EEG was also pathological. The mother and twin sisters aged 10 had a slightly increased excretion of glycin, but normal serum proline.

In the family described, one boy suffered from symptomatic hyperprolinemia; the symptoms were convulsive disorders and rash without renal disease. Another boy in the family had died, probably of the same disease. The third boy suffered from subclinical hyperprolinemia. The metabolic findings were typical hyper

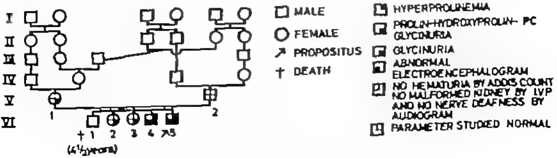

Fig. 1. Pedigree of the family described

prolinemia, hydroxyprolin-prolin-glycinuria and pyrrolidonecarboxylicacid in excess in the urine. Both girls in the family as well as the mother had slight glycinuria, and only the father was completely normal biochemically. It is possible that this disease is inherited by sexlinked, recessive mode, and the slight glycinuria is probably a heterozygotic manifestation. The explanation of this glycinuria is not clear: it is not explicable in the same way as the glycinuria in hyperprolinemic individuals.

The index patient was put on a prolin-poor diet. After a diet period of six months the serum prolin was still high, but the patient's clinical condition had improved, and the EEG was normal.

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25 Effects of Beta Adrenergic Blockade on Heart Rate and Blood Lactate in Children during Maximal and Submaximal Exercise

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Hemodynamic studies in adults with beta-adrenergic blocking agent have been reported in recent years (1, 2, 3). During submaximal work heart rate decreases 10—20 % and with unchanged stroke volume the cardiac output also decreases but with increasing A—V oxygen difference. Studies of heart rate after beta-blockade at maximal and exhausting exercise and blood lactate production have not been reported, nor any studies of the cardiac response in childhood.

Material and Method

11 healthy schoolboys in 2 age groups, 9 and 11, have been studied before and one hour after 10 mg propranolol (Inderal®) was given by oral administration before breakfast. The studies were done on 2 different days. Heart rate was recorded by ECG at rest in

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Hyperprolinemia is a rare, inborn defect of metabolism Efron (1) has demonstrated that apparently two types of this disease exist type I is a defect of proline oxidase enzyme and type II a defect of PC-dehydrogenase A description is given here of a family with four living children of which two were suffering from hyperprolinemia type II (Fig 1)

The index case a boy was admitted at the age of 6 months he had had prolonged epileptic seizures. His birth and early development were normal On admission the patient was flabby, somnolent and hyperthermic. On the second day an erythematous rash appeared The seizures subsided within three days under antiepileptic treatment. Few pathological findings were made on laboratory examination although the EEG was extremely abnormal Strong prolin hydroxyprolin and glycinuria were found in biochemical studies. The serum proline concentration was 398 mikrog/ml After the discovery of this metabolic anomaly the whole family was examined. The oldest child in the family had died at the age of 4½ years following severe convulsive disorders and progressive mental retardation from the age of 6 months. The parents and other living children were all healthy although a boy aged 7 had also had a metabolic anomaly similar to the index case. His serum proline concentration was 334 mikrog/ml The EEG was also pathological The mother and twin sisters aged 10 had a slightly increased excretion of glycin, but normal serum proline.

In the family described one boy suffered from symptomatic hyperprolinemia the symptoms were convulsive disorders and rash without renal disease Another boy in the family had died probably of the same disease The third boy suffered from subclinical hyperprolinemia. The metabolic findings were typical hyper

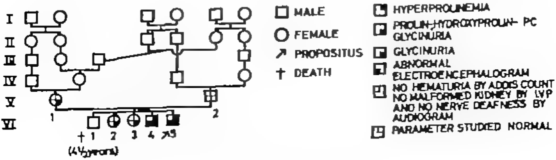

Fig 1 Pedigree of the family described.

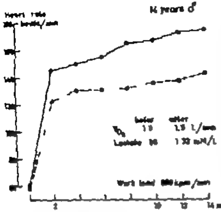

Fig. 1 Heart rate during prolonged submaximal work before and after propanolol.

the continuous increase of heart rate was diminished after propranolol (Fig 1) Despite unchanged work intensity the oxygen uptake decreased as well as the blood lactate.

In cases with abnormal orthostatic reaction per oral Inderal abolished both ECG-change and tachycardia, and has successfully been used in long term treatment.

The results show that children can perform the same exercise at submaximal and maximal intensity after beta-adrenergic blockade with significantly decreased heart rate and lesser lactate production. This means a better oxygen utilisation in the muscular metabolism and results in work on a more aerobic level.

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26 Recording of Intratracheal Pressure during Intermittent Positive Pressure Ventilation in the Newborn

E. K. VAPAAVUORI

University Children's Hospital, Helsinki

Many studies on the pressure volume relationships of normal and abnormal human lungs have been recently reported, but the intratracheal pressure changes during assisted ventilation using positive pressure respirators are not known. The purpose of this exhibit is to present some intratracheal pressure recordings correlated with clinical symptoms and X-ray findings. The pressure recordings have been obtained in 25 newborn infants re-

TABLE I *Heart Rate and Blood Lactate Before and After Beta-Adrenergic Blocking*
Mean values ± standard errors of the means are given with the significance of the differences

		Heart Rate beats/min			Blood Lactate m M/l		
		Before	*After*	*P*	*Before*	*After*	*P*
5 healthy 9-year-old boys (Height 135 ± 1.5 cm, Weight 28 ± 0,6 kg)							
Rest supine		82 ± 5.2	72 ± 3.3	< 0.02*	0.85 ± 0.06	0.88 ± 0.30	> 0.8
standing		*96 ± 6.8*	*79 ± 2.6*	*< 0.01**			
Exercise	200	138 ± 8.4	*125 ± 2.8*	< 0 2	1.29 ± 0.45	1 18 ± 0.38	> 0.8
(kpm/min)	300	159 ± 8 8	139 ± 4 4	< 0.1	1.37 ± 0.38	1.55 ± 0.73	> 0.8
	400	178 ± 8.4	157 ± 9 7	< 0 1			
	Max.	*196 ± 3 0*	*170 ± 5.3*	*< 0.02**			
1 min after		119 ± 7.9	98 ± 8.7	< 0.1	3 74 ± 2 1	2.63 ± 0 69	< 0.6
6 healthy 11-year-old boys (Height 146 ± 2.6, Weight 35 ± 1.2)							
Rest supine		88 ± 3 7	72 ± 3 6	< 0.01*	1 04 ± 0 13	0.59 ± 0.06	< 0.02
standing		103 ± 3.4	*91 ± 5 0*	*< 0 02**			
Exercise	200	*132 ± 2.1*	*111 ± 2.4*	< 0.001	1.68 ± 0.2	0.80 ± 0.09	< 0.01
(kpm/min)	300	146 ± 1.2	*124 ± 3.2*	*< 0.001****	1.85 ± 0.3	0.87 ± 0.13	< 0.05
	400	*167 ± 3.2*	*140 ± 3 1*	*< 0.001****	*2.29 ± 0.37*	*1.29 ± 0.17*	*< 0.05*
	Max.	*199 ± 1.6*	*177 ± 4 1*	< 0 001 *			
1 min. after		143 ± 6.2	113 ± 6.2	< 0 01	7 14 ± 0.74	5.33 ± 0.59	< 0.1

supine position and after 6 minutes periods on a bicycle ergometer at fixed work loads, 200 300 and 400 kpm/min Individual load was given for maximal work to exhaustion The maximal heart rate and the rate one minute after in supine position were recorded In all cases blood lactate was determined during the tests.

RESULTS

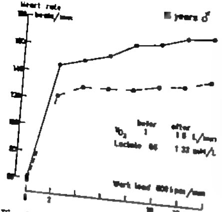
In table I the mean values of heart rate and lactate in the two groups are given The heart rate decreased significantly after propranolol, with 12—16% during submaximal work and 11—13% of the maximal heart rate. The degree of decrease was the same in both age groups and there was still a linear increase with the work load

At rest and during aerobic work the blood lactate was significantly lower in the 11 year age group after beta blockade

The maximal lactate values which were lower than in adults, decreased 29 and 25% in the two groups. The differences between mean values were, however not significant, although the individual differences were probably significant ($p < 0.05$) The systolic blood pressure during work was not significantly decreased The respiratory frequency the skin temperature and the degree of sweating were unchanged

The capacity to perform the exercise was unchanged and most of the boys found it subjectively easier to work after beta blockade

During prolonged submaximal work



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quiring artificial ventilation and treated in the Neonatal Intensive Care Unit of University Children's Hospital Helsinki

In order to measure intratracheal pressure directly an open-ended Nr 5 F feeding catheter was attached to the endotracheal tube Using the BENNETT respirators type PR 1 and PR 2 the intratracheal pressure was measured by connecting the catheter filled with saline solution to a pressure transducer an electromanometer and a recorder The recordings were obtained on systemic Bennett pressures of 20 30 and 40 cm of water and on frequencies of 40 60 and 80 cycles per minute.

According to the pressure volume characteristics and the degree of atelectasis of the lungs, significantly different types of pressure curves were recorded The shape of the pressure curve and the duration of the pressure plateau were the most marked differences between the curves in 6 different clinical syndromes. Thus intratracheal pressure recording during intermittent positive pressure breathing may be used as a diagnostic aid when severe neonatal pulmonary pathology occurs In addition, continuous monitoring of intratracheal pressure during artificial respiration is a simple and effective clinical method for demonstrating the patency of the ventilatory system

SUMMARY

Intratracheal pressure changes during artificial respiration in different types of respiratory insufficiency of the newborn were recorded and the characteristics of the pressure curves are correlated with clinical findings. It is suggested that these pressure tracings could be used for diagnostic purposes and for continuous monitoring of artificial ventilation

27 Virus Isolations from Children with Acute Respiratory Illness

A Comparison of a Family Study Group and a Group of Nursery Infants

L. VIHMA

Department of Virology and Children's Hospital, Turku University

The present study was carried out in Turku city over a period of 2 years, on two different groups.

The number of the families in the family group was 29 from September 1965 to December 1965 28 from January to March 1966 43 from April to early May 1966 42 from late May to August 1966 40 in September 1966 39 from October 1966

to early January 1967 and 38 since January 15, 1967 The number of children under school age in the family group was 59 56, 92, 89 85 84 81 respectively All the families had at least three children, the youngest one being an infant. All the infants and small children in the family group were nursed in their homes.

The other group consisted of children in a private nursery in Turku city The nursery has 15 beds. During the observation period from September 1965 to May 1967 a total of 50 infants were resident.

For virus isolation pharyngeal swabs were taken at the beginning of each respiratory illness. Specimens were inoculated directly into cell culture tubes. Two tubes of HeLa, primary monkey kidney and U cells were inoculated with each specimen. Tissue culture tubes were incubated at 35 C for two weeks. A clinical examination and diagnosis of each child was made

A total of 311 virus isolations were made of 532 cases of respiratory illness reported (24 % positive) From the family group 381 respiratory illnesses were reported with 84 virus isolates (22% positive) From the nursery group 171 illnesses were reported with 48 virus isolates (27% positive)

Among the agents isolated in the family group were respiratory syncytial (RS) virus (22 strains) parainfluenza type 3 (11 strains) adenovirus type 1 (12 strains) adenovirus type 2 (6 strains) adenovirus type 3 (7 strains) adenovirus type 5 (5 strains) adenovirus type [illegible] (3 strains) adenovirus type 7 (4 strains) and herpes simplex (7 strains)

In the nursery group the isolates were RS virus (14 strains) parainfluenza type 3 (1 strain) adenovirus type 1 (7 strains) adenovirus type 2 (11 strains) adenovirus type 5 (12 strains) adenovirus type 6 (2 strains) and Coxsackie B_3 (4 strains) RS virus was isolated simultaneously with adenovirus, type 2 or type 5, in 2 cases from the family group and in 4 cases from the nursery group

RS virus isolates in the family group were obtained during the autumn both in 1965 and in 1966 and in 1967 during the first three months but in the nursery group only in February 1967 Parainfluenza type 3 was isolated in the spring of 1966 in both groups but in the autumn of 1966 only in the family group Adenovirus types 1 2 and 5 were isolated in both study groups. The epidemic of adenovirus type 3 in the family group did not occur in the nursery Neither was adenovirus type 7 isolated in the nursery group

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STUDIES ON RESPIRATORY SYNCYTIAL VIRUS INFECTION

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From the Department of Virology University of Turku
Finland

STUDIES ON RESPIRATORY SYNCYTIAL VIRUS INFECTION

by

Bo Berglund

The present paper is based on the following studies

I. BERGLUND, B., VIHMA, L. and WICKSTRÖM, J. Respiratory syncytial virus studies on children hospitalized during an outbreak of respiratory illness in Finland. *Amer J Epidem*, 81 271 1965.

II. BERGLUND, B., FORSSELL, P. and HALONEN-NORONEN, M. An outbreak among children of respiratory illness caused by respiratory syncytial virus. A serological and clinical study. *Acta Paediat Scand*, 54 519 1965.

III. BERGLUND, B. and MANTYJARVI, R. Respiratory infections in children in ... in Finland. Virologic and epidemiologic studies over ... 21-month period. *A... Paediat Fenn*, 12 143, 1966.

IV. BERGLUND, B., SALMIVALLI, A. and TOIVANEN, P. Isolation of respiratory syncytial virus from middle ear exudates of infants. *Act Otolaryng (Stockholm)* 61 475, 1966.

V. BERGLUND, B., SALMIVALLI, A., TOIVANEN, P. and WICKSTRÖM, J. Isolation of respiratory syncytial virus from middle ear exudates of infants. *Arch Dis Child*, 41 554, 1966.

VI. BERGLUND, B., KOUTANEN, A. E. and LAURÉN, P. Experimental inoculation of guinea pig's middle ear with respiratory syncytial virus. *Ann Med Exp Fenn*, 44 ..., 1966.

VII. BERGLUND, B., KOUTANEN, A. E. and LAURÉN, P. Experimental inoculation of guinea pig's middle ear with respiratory syncytial virus. *Act Otolaryng (Stockholm)*. In press.

VIII. BERGLUND, B. and STRÖHLMANN, C. H.: Respiratory syncytial virus infections in hospitalized children. Evaluation of the virus isolation and complement fixation techniques in the virological diagnosis. Clinical and epidemiological characteristics. *Acta Paediat Scand*, 56 369 1967.

IX. BERGLUND, B. Respiratory syncytial virus infections in families. A study of family members of children hospitalized for acute respiratory disease. *Acta Paediat Scand*, 56 1967 In press.

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XI. BERGLUND, B., SALMIVALLI, A. and GRONROOS, J. A. The role of respiratory syncytial virus in otitis media in children. *Act Otolaryng (Stockholm)* 63 1967 In press.

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INTRODUCTION

Since severe acute respiratory disease in infants is a worldwide public health problem which has far exceeded that of poliomyelitis and many other infectious illnesses in mortality it is clear that an understanding of the etiology and epidemiology of this disease is of primary importance. Over the past 15 years, advances in laboratory methodology have contributed to the discovery and classification of a large number of hitherto unrecognized nonbacterial pathogens from the respiratory tract. The respiratory syncytial (RS) virus was isolated in 1956 and its importance in acute human respiratory disease was definitely documented a few years later It has proved the most important single cause of pneumonia and bronchiolitis in infants and small children.

The present paper is intended to provide information on the incidence, prevalence and spread of RS virus infection in an urban community in Finland (Turku) and also to some degree in the capital of the country (Helsinki) It also describes respiratory and otological disease manifestations due to infection with RS virus. The experimental studies to be presented were concerned with the question of reproduction of RS virus in the guinea pig middle ear with the development of a method of producing specific hyperimmune RS virus antiserum, and with the specific precipitin response following inoculation of the agent.

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REVIEW OF THE LITERATURE

Discovery of the virus: first isolation from man; isolation from unfrozen specimens

In 1956 Morris and associates (46) described the first recovery of a virus, which they termed chimpanzee coryza agent (CCA), from the respiratory secretions of laboratory chimpanzees with coryza and established a presumptive etiological association between the new agent and the acute respiratory illness of a laboratory worker who had had close contact with the animals. The next year *Chanock and his associates* (14, 18) reported the isolation of two virus strains, indistinguishable from CCA, from infants with lower respiratory tract infection and suggested these isolates and the CCA be grouped together and named the respiratory syncytial (RS) virus. In 1960 Beem *et al.* (9) observed that the recovery of RS virus from throat swabs is highly facilitated when the specimens are inoculated into tissue culture without prior freezing and thawing and by this means succeeded in isolating the agent from not less than 41 patients with acute respiratory illness.

Laboratory diagnosis

The diagnosis by virus isolation is usually made by culturing the agent from a sample of *throat secretion*. Several studies of subjects with acute respiratory infection (1, 5, 9, 12, 15, 27, 35, 43, 57, 59) show that RS virus may be recovered with high frequency from young children, and with the highest frequency from infants in the first 6 months and year of life, and thereafter more rarely with increasing age. Some researchers (1, 9, 43, 57) have recovered the agent infrequently or not at all from children of more than approximately 5 to 6 years of age. It is not known whether this indicates less likelihood of isolating RS virus from older infected children, or whether the infection rates of older children are very much lower.

The first RS virus isolation from an adult person was reported by Beem *et al.* (9) *who recovered the virus from* a 35-year-old man. Subsequently Hamre and her associates (32, 33) succeeded in isolating RS virus from 15 medical students with common colds. Johnson and his associates (37) recovered 4 strains of RS virus from recruits in an infantry training regiment. In a study of human adult volunteers experimentally infected with the agent, virus shedding was noticed in a considerable number of cases (38, 40). Jamieson *et al.* (36) reported positive isolations from 3 adult persons of whom *the oldest was 76 years old. These and* other studies (6, 39) indicate that adults and children may acquire symptomatic RS virus reinfection with associated positive isolations despite the presence in

the serum of specific neutralizing antibody to a moderate or high titer. Likewise it has been shown that young infants are susceptible to RS virus and may acquire primary infection and shed virus despite the presence of circulating specific neutralizing antibody transmitted from the mother (11). Chanock stated (16) that the inability of the serum neutralizing antibody to effectively prevent and modify RS virus infection depends on the property of this agent to spread and replicate primarily in the superficial epithelium of the respiratory tract.

The complement fixation (CF) test has been employed more extensively than the neutralization test as a serodiagnostic method of detecting RS virus infection because of its greater simplicity and ease of performance. Both tests have proved somewhat insensitive as a means of demonstrating infection in young infants under 3 to 6 months of age (7, 9, 14, 15, 28, 47, 60). Studies show that the neutralization test is more capable than the CF test in detecting diagnostic antibody rises in children in this young age group (14, 15, 47), but that the sensitivity of the latter can be improved by increasing the amount of CF antigen from 4 to 8 units (15, 39, 51). Ross et al. (51) emphasized the importance in obtaining a good CF antigen of incubating the tissue cultures for prolonged periods after the development of the complete cytopathic effect, and moreover stated that the optimal time for the collection of convalescent serum from very young infants is between the 4th and 6th week of illness. Chanock et al. (14) pointed out the necessity of a low initial serum dilution of preferably 1/4 or 1/2 in the titration of CF antibody in sera from young children.

RS virus infection in adults may not always be accompanied by a measurable serological response. Out of 30 adult volunteers who contracted infection as indicated by positive isolations after intranasal administration of RS virus, 12 failed to develop increased antibody titers (38). In the study of natural RS virus infections among college students (33), 4 subjects from whom virus was recovered likewise showed no increase in antibody. In both these studies, the antibody responses occurred predominantly in subjects who developed clinical illness. According to Johnson et al. (38), there seems to be an association between the extent of RS virus infection in adults as measured by the serological response and the occurrence of respiratory disease. The CF and neutralization tests have proved roughly equally reliable in the serodiagnosis of adult RS virus infection (33, 38). It is noticeable that the adult volunteers did not show significant rises in antibody titer until 14 to 18 days after inoculation (38).

Antigenic strain variations

Experimental studies and studies of human convalescent sera have shown that different RS virus strains share a common CF antigen (20, 2?, 57, 60). This has highly facilitated serodiagnostic procedures using the CF technique, since potent CF antigen prepared from any strain can be expected to have the capacity of fixing complement with the antibody formed in the course of every RS virus infection.

However, antigenic differences do oc

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RS virus infection and respiratory ill ness in a study comprising children from an outpatient clinic. Later Beem *et al.* (9) confirmed this observation additionally providing evidence that RS virus infection is etiologically firmly associated with respiratory illness and particularly with bronchiolitis and pneumonia in infants. The important role of this agent as a cause of upper and lower respiratory disease in infants and children has subsequently been documented in a series of investigations (8, 15 17 23 30 44, 47 49 52) Kapikian *et al.* (39) showed that RS virus pneumonia occurs about equally as often in infants with pre-illness neutralizing antibody as in those without Hilleman *et al* (34) and Chanock *et al* (16) who estimated the relative importance of various viruses in acute respiratory disease showed, in studies extending over a period of several years, that RS virus is apparently responsible for the greatest part of total respiratory illness in infancy and early childhood. They concluded that this agent is the most important single definable viral pathogen in the respiratory tract during early life

RS virus has proved the most common definable agent in the bronchiolitis syndrome (2, 5 8, 9 1 15 17 41 43 47—50 53) According to Chanock (16) it also causes pneumonia more frequently than other viruses, bronchitis and upper respiratory infection to about the same extent as a number of other viral agents, but croup comparatively infrequentl RS virus has been shown to produce respiratory disease with highest frequency during the first 6 months of life a unique property not shared by other respiratory pathogens (16)

Holzel *et al.* (35) cultured *Haemophilus influenzae* significantly more frequently from children with RS virus infection than from other groups of subjects. However bacteriological examinations carried out in a number of other studies (8 9 14, 44 46 47 49 55) have failed to reveal data which would establish any causal connection between a bacterial pathogen and the development of bronchiolitis or pneumonia in subjects infected with RS virus. These findings are in agreement with the observation of Field *et al.* (25) in a double-blind trial, that treatment with antibiotics did not accelerate or otherwise influence the recovery of children from epidemic bronchiolitis etiologically linked with RS virus.

Deaths have been reported among infants of 12 months of age or younger with confirmed or probable RS virus infection (—4 9 16 21 26 27 35 41) A review reveals that 26 % of all the children who died were also suffering from some abnormal complication such as congenital heart disease mongolism or burns. According to Cortes and Chanock (21) the mortality rate may be as high as 2.4 % among RS virus-positive hospitalized patients.

Since maternal RS virus antibodies are apparently transmitted to the newborn (7 14 28 30 44) 50 % or more of all infants less than 3 months old are mainly for this reason seropositive to RS virus. After the disappearance of the maternal antibodies by the 4th to 8th month of age, the proportion of seropositive individuals increases with age About 80 to 100 % of 4 to 6 year-old children have neutralizing antibody for RS virus (7 14 30 4., 54 57 59) These

cur between strains of RS virus, as demonstrated in cross neutralization tests with ferret sera obtained 3 to 4 weeks after inoculation of virus by the intranasal route (20 22) In these experiments by Coates and her associates, animals infected with the prototype (Long) RS virus, isolated in 1956 developed homologous neutralizing antibody titers which were 4 to 64 fold higher than titers to a strain (CH 18537) isolated in 1962. The antigenic differences were reciprocal as 3 out of 4 animals infected with the CH 18537 strain developed no detectable heterologous antibody although the homologous titers were 1/32 to 1/64 Reinfection of the animals with the homologous strain resulted in the development of heterologous antibody with little or no change in the homologous antibody titer The existence of antigenic differences between RS virus strains was subsequently again demonstrated by Wulff et al (60) in cross neutralization tests with rabbit and monkey sera obtained after parenteral virus inoculations. However in contrast to Coates et al (20 22) these investigators never achieved an increase in the low titer to the heterologous strain even after 3 reimmunization cycles. Using sera obtained from guinea pigs inoculated with virus by the intranasal route Suto et al (57) recently demonstrated antigenic dissimilarities between the Long strain of RS virus and a strain isolated in Japan Antigenic analysis of RS virus isolates by the plaque reduction neutralization test using post infection ferret sera has shown that most isolates, although reasonably closely related can be distinguished from each other but that there are some strains, such as the CH 18537 isolated in the U.S.A. and the 8/60 strain isolated in Gothenburg Sweden which differ essentially by reason of their antigenic properties from most of the other RS viruses studied (19 24) It is of interest to note that several antigenically distinguishable RS viruses may be active during the same outbreak. Coates et al (19) detected no less than 3 antigenically distinguishable patterns among 12 strains isolated during a single epidemic in the U S.A. in 1964 The Randall strain used throughout the present study and the Long strain have proved antigenically identical or closely related (9 10 24)

While ferrets and guinea pigs respond to primary instranasal RS virus inoculation by the development of homologous but not heterologous neutralizing antibody infants primarily infected with RS virus presumably develop both homologous and heterologous antibody This contention is based upon the observation by Wulff et al (60) and Ross et al (51) that young infants with probable primary RS virus infection produce significant amounts of neutralizing antibody against both the local and prototype strains. However in most cases the antibody showed somewhat higher titers for the local strain On the basis of their antigenic analysis of RS virus, Coates et al (19) concluded that the agent apparently resembles the A or A famlies of influenza A virus in the extent of antigenic heterogeneity

Importance in etiology of acute respiratory illness

Chanock and Finberg (14) first suggested the association between human

OBJECT OF THE STUDY

The studies on human subjects dealt with

- the incidence of RS virus infection over a prolonged period of study among children in an urban community (Turku) in Finland (I, III VIII XI)
- the symptoms and signs in RS virus-infected hospitalized children the division of these children into various disease categories by age, and into various groups according to place of residence prior to admission (I II VIII)
- the relative importance of RS virus-associated severe acute respiratory disease as an indication for hospitalization during outbreaks caused by this agent among children in Finland (I II III VIII)
- the evaluation of the virus isolation technique using a direct inoculation method as compared with the CF test as a means of detecting RS virus infection in children of various ages (I VIII)
- the numbe f solation specimens required for a positi e diagnosis, and the proportion of specimens yielding virus at various phases of disease (VIII)
- the role of RS virus in otitis media in children (IV V VIII XI)
- the incidence and spread of RS virus infection among the children of a selected nursery over a prolonged period of study (III)
- the occurrence and spread of RS virus infection in families (IX)

The experimental studies carried out concentrated on

- the susceptibility of the guinea pig middle ear to RS virus, and the development of a virus isolation technique suitable for studies of the otological significance of this virus (VI VII)
- the development of a convenient method of producing high titered RS virus antiserum free from undesired antibody (X)
- the occurrence of precipitating antibodies to RS virus and the identification of the precipitation lines formed by these antibodies (X)

percentage rates apparently represent a minimum estimate of experience gained with the agent during previous years.

Although the role of RS virus in childhood respiratory disease is fairly well understood comparatively little is known regarding the consequences of infection in adults. RS virus reinfection in adults seems to be associated with a mild mostly afebrile illness of the common cold type in the upper respiratory tract (32 33 37 38 40) The data available suggests that adult RS virus infection is relatively infrequent (34) and presumably comparatively unimportant but that it may cause discomfort of clinical significance under certain conditions According to Sommerville (55) and Carilli *et al* (13) RS virus may have a causal or associated role in exacerbations of chronic bronchitis.

Spread of infection

Epidemics of RS virus infection have been reported in a number of countries in North America Europe Australia and Asia. The epidemics usually sharply limited in length and of 2 to 5 months duration, have been reported as recurring at approximately yearly intervals during the fall winter and spring among urban populations, and affecting a great number of infants and young children. According to findings in various parts of the world the peak in serious acute pediatric respiratory disease particularly the peak in bronchiolitis and pneumonia in small infants, coincides annually with the prevalence of RS virus infection (16 17 26 29 47)

Little is known about the conditions for the spread of RS virus at work or among separate groups of people in public life, and the infection risk they are exposed to However RS virus is known to obtain entrance during epidemics to certain institutions such as the nurseries and premature nurseries and to spread quickly among the young occupants with resultant infection rates ranging from 80 to 100 % (11 39 56) Hospital spread of RS virus infection has been shown to occur among pediatric control in patients, as reported by Chanock *et al* (14 15) with infection rates of 42 and 15 % respectively In other studies (9 44) hospital-acquired RS virus infections have been uncommon.

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- the incidence and spread of RS virus infection among the children of a selected nursery over a prolonged period of study (III)
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The experimental studies carried out concentrated on

- the susceptibility of the guinea pig middle ear to RS virus, and the development of a virus isolation technique suitable for studies of the otological significance of this virus (VI VII)
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Although the role of RS virus in childhood respiratory disease is fairly well understood comparatively little is known regarding the consequences of infection in adults. RS virus reinfection in adults seems to be associated with a mild mostly afebrile illness of the common cold type in the upper respiratory tract (32 33 37 38 40) The data available suggests that adult RS virus infection is relatively infrequent (34) and presumably comparatively unimportant but that it may cause discomfort of clinical significance under certain conditions According to Sommerville (55) and Carilli *et al* (13) RS virus may have a causal or associated role in exacerbations of chronic bronchitis.

Spread of infection

Epidemics of RS virus infection have been reported in a number of countries in North America, Europe Australia and Asia. The epidemics, usually sharply limited in length and of 2 to 5 months duration have been reported as recurring at approximately yearly intervals during the fall winter and spring among urban populations, and affecting a great number of infants and young children According to findings in various parts of the world, the peak in serious acute pediatric respiratory disease particularly the peak in bronchiolitis and pneumonia in small infants, coincides annually with the prevalence of RS virus infection (16 17 26 29 47)

Little is known about the conditions for the spread of RS virus at work, or among separate groups of people in public life and the infection risk they are exposed to. However RS virus is known to obtain entrance during epidemics to certain institutions such as the nurseries and premature nurseries, and to spread quickly among the young occupants with resultant infection rates ranging from 60 to 100 % (11 39 56) Hospital spread of RS virus infection has been shown to occur among pediatric control in patients, as reported by Chanock *et al* (14 15) with infection rates of 42 and 15 % respectively In other studies (9 44) hospital acquired RS virus infections have been uncommon.

OBJECT OF THE STUDY

The studies on human subjects dealt with

- the incidence of RS virus infection over a prolonged period of study among children in an urban community (Turku) in Finland (I, III VIII XI)
- the symptoms and signs in RS virus-infected hospitalized children, the division of these children into various disease categories by age, and into various groups according to place of residence prior to admission (I, II VIII)
- the relative importance of RS virus-associated severe acute respiratory disease as an indication for hospitalization during outbreaks caused by this agent among children in Finland (I II, III VIII)
- the evaluation of the virus isolation technique using a direct inoculation method as compared with the CF test as a means of detecting RS virus infection in children of various ages (I VIII)
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LABORATORY DIAGNOSIS (I, II, III, VIII, IX)

Material and methods

The subjects studied were hospitalized children under 6 years (I VIII) or under 2 years (II) of age. Throat swab specimens were obtained with a dry cotton applicator which was immediately immersed in the maintenance medium of a tissue culture tube after which the fluid remaining in the cotton was pressed out by rubbing the swab along the inner surface of the tube. This method here referred to as the direct inoculation technique was employed throughout the study with minor variations. In the first study (I) 1 applicator alone was used for inoculating 2 tissue culture tubes (BS C1 cells in 5 % calf serum) whereas in the second study (II) 2 tissue culture tubes (U cells in 5 % horse serum) were inoculated each with a separate applicator. Inoculated BS-C1 cultures were examined every alternate day for a period of 4 weeks, and inoculated U cultures every day or every alternate day for a period of 2 weeks.

Variations in CF techniques and blood sampling intervals are apparent from the data listed below.

Results and discussion

The direct inoculation technique seemed disappointing at the beginning of the study (I) since heavy growth of fungi occurred in the inoculated tissue cultures. However it soon appeared that the concentration of amphotericin B (0.025 microg/ml) used was insufficient. After the addition of nystatin (25 units/ml) to the maintenance medium, not a single culture out of the 200 tested (I) was lost because of fungus growth. The concentration of nystatin was subsequently maintained at the level of 25 units/ml, and that of amphotericin B increased to 5 microg/ml (VIII). The presence of the latter drug might have been unnecessary. In any case no fungal contamination was observed when these two antimycotic drugs were used in the concentrations given, and no toxic effect on the tissue cultures was apparent. Overgrowth of bacteria occurred sometimes despite the presence of penicillin and streptomycin in the culture media. About 1 % of the tubes had to be discarded for this reason (I).

The method of inoculating cell cultures

Study No.	Scale	End points. Per cent hemolysis	Units of test antigen	Initial serum dilution	Interval in weeks between 1st and 2nd serum
I	Macro	25	8	1/8	1—2
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VIII	Micro	25	3	1/4	1—

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The time required for the cytopathic effect (CPE) to become apparent following inoculation of throat swab material varied from 8 to 25 days (mean time 13 days) for the BS-CI cultures (I) and from 3 to 14 days (mean time 6 days) for the U cultures (VIII). Eighty % of the positive U cultures showed a definite CPE within 1 week following inoculation. Although virus growth was probably promoted more efficiently in the U cells due to minor dissimilarities in inoculation and feeding techniques, it is difficult to explain the remarkably faster appearance of CPE in the U cultures solely on the basis of these differences in technique. Characteristically the CPE of the BS-CI cultures consisted mostly of localized syncytial areas, whereas the CPE of the U cultures, for the most part, caused destruction of the entire cell sheet.

Detailed analysis of the isolation results obtained after direct inoculation of U cultures with throat swabs (VIII) revealed that:

1) the likelihood of detecting RS virus infection in children under 6 years of age was highest during the first week of illness (82 % positive specimens) the rate of positive specimens then decreasing during the second (49 %) third (21 %) and fourth (11 %) weeks of illness.
2) all children found to be positive by virus isolation, harboured virus in their throat secretions as early as on the first day of specimen collection, indicating that repeated sampling during subsequent days was unnecessary
3) for a positive diagnosis by virus isolation it was necessary to inoculate more than 1 tissue culture tube (each with a separate swab) The necessity of inoculating more than 1 tissue culture tube was more apparent during the later course of the disease, but even at the acute stage the inoculation of tubes appeared desirable. As many as 14 % of the RS virus infections diagnosed by virus isolation could have remained undetected,

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had only 1 throat swab been taken from each child shortly after hospitalization for the inoculation of only 1 tissue culture tube.

In the first study (I) virus isolation specimens were obtained from 76 children all of whom had acute respiratory illness RS virus was isolated from 7 out of 11 (64 %) subjects with bronchiolitis, 7 out of 14 (50 %) with pneumonia 6 out of 28 (21 %) with bronchitis and 3 out of 23 (13 %) with infection of the upper respiratory tract Similar results have been obtained by other investigators (9 15) all indicating the association of severe respiratory disease with RS virus infection. It can be noted that the association rate was highest for the bronchiolitis syndrome which is again in agreement with the findings of others (9 15 17) The rate of positive isolations decreased with age, as also shown previously (9 15 47) A noticeable feature was that the agent was recovered from no less than 5 out of 7 (70 %) of the infants under 3 months of age suggesting its importance as a cause of infection in the first stages of life (I)

The documented low titered and slow antibody response of very young infants to RS virus infection was also investigated to some degree in the present study (I II) In the first study (I) none of the <3 month-old subjects showed significant (4-fold or greater) rises in CF titer for RS virus, although an RS virus isolation was obtained from some of them. These findings are not surprising as the interval between the paired serum specimens was only 1 to 2 weeks and the serum titrations were initiated from a comparatively high (1/8) dilution. In the second study (II) which was for the main part a serological study the s[…] were collected at an identical inter[…] but the CF titrations were initiat[…] from a 1/4 dilution Of the 25 infa[…] of <3 months of age tested, 3 (12 %[…] showed a significant CF antibody r[…]sponse to RS virus. However not ev[…] this number would have shown a signi[…]icant rise in titer had the serum titration been initiated from a 1/8 dilution, since the convalescent titers never exceeded 1/8. In contrast the convalescent titers of the children of 1 year or over always exceeded 1/8 A comparison revealed that 19 subjects out of 35 (54 %) in the age group 3 — <6 months had significant titer rises, as compared with 26 out of 39 (67 %) in the age group 6 — <12 months and 11 out of 20 (55 %) in the age group 12 — <24 months. The actual rate of RS virus infection among those of <3 months of age remained unknown as virus isolation specimens were not taken but was probably higher than the 12 % observed. The fact that no less than 8 of the <3 month-old infants developed a weak rise in titer from $<1/4$ to 1/4 or from 1/4 to 1/8, speaks in favor of this assumption. On the basis of the results it could be concluded that convalescent serum specimens should not be obtained from infants of <3 months of age, before the 5th week of illness, and that titration of their RS virus CF antibody should preferably be initiated from a serum dilution of 1/4 or lower

In a study of the family members of children with RS virus infection (IX) 7 parents were shown to develop significant CF antibody titer rises to the agent of from $<1/4$ to 1/8 or from $<1/4$ to 1/16 With the reservation that

the paired sera were possibly not appropriately timed and that the number of cases with significant rises in titer was small, the findings demonstrate a surprisingly low-titered CF antibody response to RS virus infection in adults in the age group 20 to 30 years.

The relation between the concentration of antigen required for optimal sensitivity of the CF test and the age of the subjects studied was not investigated in the present study. However, one observation was made with relevance to this question (III). Appropriately timed sera from 10 nursery infants with verified RS virus infection (positive virus isolations) were examined for CF antibody to RS virus in the same test. Nine of the children were most probably suffering from primary infection and were under 4 months of age. One was 4 months old and had a proved reinfection. By accident, the sera were tested with an antigen clarified by centrifugation and stored at +4 C for several months having lost most of its CF activity. This antigen failed to fix complement with the convalescent sera from the 9 primarily infected children, but revealed a rise in titer from < 1/4 to ≧1/64 in the reinfected child. These findings suggest, that besides age, previous experience with the agent may also be a factor determining the concentration of antigen required in the CF test.

Attempts were made to estimate the sensitivity of the isolation method and the CF test as a means of detecting RS virus infection (I, VIII). The results of the latter study (VIII) will be dealt with in more detail. In order to render the CF method more sensitive, a third serum specimen was collected from a great proportion of the < 6 month-old subjects about 5 weeks after the initial one, and 8 antigen units were employed in the tests. As previously outlined, 2 U cell cultures were directly inoculated, each with one of 2 throat swabs, shortly after admission. A retrospective study revealed that out of 22 children of 3 months to < 6 years of age with a significant rise in CF titer 19 (86 %) had a positive virus isolation. Of the 3 CF positive children who failed to yield virus, one was 3 months old and already at the convalescent phase of infection at the time of sampling, the age of the 2 others being 5 years. The findings seem to reflect increasing difficulties in isolating RS virus from children of 5 years or over and are, in this respect, in agreement with the experience of others (1, 43, 57). On the basis of the results it would appear that the efficiency of the isolation method used in the present study in detecting acute RS virus infection in children under 6 years of age is between 86 and 100 %.

To determine the diagnostic efficiency of the CF test, 22 children of from 1 month to < 6 years of age with positive RS virus isolations were kept under observation for the development of a subsequent rise in titer. Nineteen developed a significant antibody response, while 3 failed to do so. The latter were 1, 2 and 11 months old respectively. The results showed a diagnostic efficiency for the CF test of 86 % for all children (similar to that of the isolation method) and of 100 % for those of 1 year or over. The isolation method was thus highly efficient in detecting infection in subjects under 5 years, and the CF test in subjects of 1 year or over.

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The relation between the concentration of antigen required for optimal sensitivity of the CF test and the age of the subjects studied was not investigated in the present study. However, one observation was made with relevance to this question (III). Appropriately timed sera from 10 nursery infants with verified RS virus infection (positive virus isolations) were examined for CF antibody to RS virus in the same test. Nine of the children were most probably suffering from primary infection and were under 24 months of age. One was 24 months old and had a proved reinfection. By accident, the sera were tested with an antigen clarified by centrifugation and stored at +4 C for several months having lost most of its CF activity. This antigen failed to fix complement with the convalescent sera from the 9 primarily infected children, but revealed a rise in titer from <1/4 to ≧1/64 in the reinfected child. These findings suggest, that besides age, previous experience with the agent may also be a factor determining the concentration of antigen required in the CF test.

Attempts were made to estimate the sensitivity of the isolation method and the CF test as a means of detecting RS virus infection (I, VIII). The results of the latter study (VIII) will be dealt with in more detail. In order to render the CF method more sensitive, a third serum specimen was collected from a great proportion of the <6 month-old subjects about 5 weeks after the initial one, and 8 antigen units were employed in the tests. As previously outlined, 2 U cell cultures were directly inoculated, each with one of 2 throat swabs, shortly after admission. A retrospective study revealed that out of 22 children of 3 months to <6 years of age with a significant rise in CF titer 19 (86 %) had a positive virus isolation. Of the 3 CF positive children who failed to yield virus, one was 3 months old and already at the convalescent phase of infection at the time of sampling, the age of the 2 others being 5 years. The findings seem to reflect increasing difficulties in isolating RS virus from children of 5 years or over and are, in this respect, in agreement with the experience of others (1, 43, 57). On the basis of the results it would appear that the efficiency of the isolation method used in the present study in detecting acute RS virus infection in children under 5 years of age is between 86 and 100 %.

To determine the diagnostic efficiency of the CF test, 22 children of from 1 month to <6 years of age with positive RS virus isolations were kept under observation for the development of a subsequent rise in titer. Nineteen developed a significant antibody response, while 3 failed to do so. The latter were 1, 3 and 11 months old respectively. The results showed a diagnostic efficiency for the CF test of 86 % for all children (similar to that of the isolation method) and of 100 % for those of 1 year or over. The isolation method was thus highly efficient in detecting infection in subjects under 5 years, and the CF test in subjects of 1 year or over.

had only 1 throat swab been taken from each child shortly after hospitalization for the inoculation of only 1 tissue culture tube.

In the first study (I) virus isolation specimens were obtained *from 76 children*, all of whom had acute respiratory illness. RS virus was isolated from 7 out of 11 (64 %) subjects with bronchiolitis, 7 *out of 14 (50 %)* with pneumonia 6 out of 28 (21 %) with bronchitis and 3 out of 23 (13 %) with infection of the upper respiratory tract. Similar results have been obtained by other investigators (9 15) all indicating the association of severe respiratory disease with RS virus infection. It can be noted that the association rate was highest for the bronchiolitis syndrome, which is again in agreement with the findings of others (9 15 17). The rate of positive isolations decreased with age as also shown previously (9 15 47). A noticeable feature was that the agent was recovered from no less than 5 out of 7 (70 %) of the infants under 3 months of age, suggesting its importance as a cause of infection in the first stages of life (I).

The documented low titered and slow antibody response of very young infants to RS virus infection was also investigated to some degree in the present study (I II). In the first study (I) none of the < 3 month-old subjects showed significant (4-fold or greater) rises in CF titer for RS virus, although an RS virus isolation was obtained from some of them. These findings are not surprising as the interval between the paired serum specimens was only 1 to 2 weeks and the serum titrations were initiated from a comparatively high (1/8) dilution. In the second study (II) which was for the *main part a* serological study the sera were collected at an identical interval but the *CF* titrations were initiated from a 1/4 dilution. Of the 25 infants of < 3 months of age tested, 3 (12 %) showed a significant CF antibody response to RS virus. However not even this number would have shown a significant rise in titer had the serum titration been initiated from a 1/8 dilution since the convalescent titers never exceeded 1/8. In contrast the convalescent titers of the children of 1 year or over always exceeded 1/8. A comparison revealed that 19 subjects out of 35 *(54 %)* in the age group 3 — < 6 months had significant titer rises, as compared with 26 out of 39 (67 %) in the age group 6 — < 12 months and 11 out of 20 (55 %) in the age group 12 — < 24 months. The actual rate of RS virus infection among those of < 3 months of age remained unknown as virus isolation specimens were not taken, but was probably higher than the 12 % observed. The fact that no less than 8 of the < 3 month-old infants developed a weak rise in titer from < 1/4 to 1/4 or from 1/4 to 1/8 speaks in favor of this assumption. On the basis of the results it could be concluded that convalescent serum specimens should not be obtained from infants of < 3 months of age, before the 5th week of illness, and that titration of their RS virus CF antibody should preferably be initiated from a serum dilution of 1/4 or lower.

In a study of the family members of children with RS virus infection (IX) 7 parents were shown to develop significant CF antibody titer rises to the agent of from < 1/4 to 1/8 or from < 1/4 to 1/16. With the reservation that

fection occurred in the nursery (III) each coinciding in time with the RS virus epidemics in the city and involving a minimum of 58 % and 83 % of the occupants respectively. During an RS virus epidemic in the city of Helsinki extending from December 1963 to about February 1964 (II) infants in 3 residential nurseries were sampled in order to discover whether they possibly had RS virus infection; the occupants in both localities were found to be heavily infected with the agent. The importance of the RS virus as a cause of respiratory disease among nursery groups of children was subsequently further evaluated in another study (VIII). Of the subjects hospitalized for disease due to the agent, 44 % were day nursery children whereas among those hospitalized during the same time for infections due to respiratory pathogens other than RS virus, the proportion of children in this category was only 8 % ($p < 0.01$).

Another of the epidemiological characteristics of the RS virus infection seemed to be its tendency to occur in families (IX). The agent was a common cause of infection among the members of 25 families, leaving 23 other control families, with one exception, unaffected. Of the members of the RS virus infection-positive families, the adult subjects showed rising titers, whereas the children showed either rising titers or titers which had already reached a high level. On the basis of these results it was suggested that RS virus was not brought into the family by the adult members (the parents) but by some of the children.

In Table 1 3 strains of RS virus are compared with a fourth one. The Randall strain, isolated by Beem *et al.* in the U.S.A. in December 1958 (9). As can be seen, the Anderson strain showed antigenic similarities to the Randall strain, unlike the two other strains.

Discussion

The RS virus epidemics recorded in the city of Turku were roughly of 8

TABLE 1. *Comparison of the antigenic properties of 4 strains of respiratory syncytial virus in a neutralization test with guinea pig Randall strain antiserum.*

Strain	TCD_{50} units of virus	CPE Serum dilution 1/64	1/512
Randall	10^{4}	—	+
(1954, USA)	10[illegible]	—	—
Anderson	10[illegible]	—	++
(Dec 1963)	10[illegible]	—	—
Helm	10[illegible]	+	++++
(June 1963)	10[illegible]	—	++
Turku	10[illegible]	+	++++
(Oct 1963)	10[illegible]	—	+

Obtained after 1 intranasal and 2 intracardiac virus inoculations; CF titer 1/[illegible] neutralization titer 1/2048 as determined against 10[illegible] TCD_{50} units of the Randall strain.

EPIDEMIOLOGY (I, II, III, VIII, IX, XI)

Methods

Continuous surveillance was maintained during the period September 1963 to December 1966 on the incidence of RS virus infection among the pediatric population of the city of Turku. This surveillance consisted predominantly of a search for RS virus in throat swabs and rising CF antibody titers to the agent in paired serum specimens delivered from the Hospital for Infectious Diseases in the city Comparison of the antigenic properties of RS virus strains from different epidemics was carried out according to a neutralization technique described in study No X. The test was read after 4 days.

Results

Four fairly sharply limited outbreaks of RS virus infection occurred in the city The first one extended from November 1963 to January 1964 the second from April to June, 1965 the third from September to November 1965 and the fourth from October to December 1966 In the inter-epidemic periods there were no positive RS virus isolations or serological evidence of infection with the agent. Each of the epidemics were approximately of 2½ to 3 months duration The localization of the epidemics in time indicates that RS virus was prevalent in the community each year but at irregular intervals varying from 3 months to 1 year and 2 months.

Studies on children under 6 years of age admitted to the Hospital for Infectious Diseases during 2 month study periods throughout the duration of the first and second RS virus epidemics revealed that the RS virus infections were on each occasion differently distributed according to age In the course of the first outbreak (I) the total number of children admitted for acute respiratory disease was 87 of whom 30 % were suffering from RS virus infection. Infections with the agent were particularly common in the youngest age groups, with the highest frequency (75 %) occurring among infants under 3 months of age the infection rate being only 9 % in the 2 to <6 year-old group During the second outbreak (VIII) a total of 60 subjects were admitted of whom not less than 57 % had RS virus infection. RS virus infection was on this occasion most frequent in the age group 3 to <6 months (infection rate 100 %) but was also common among older children, the 2—<6 year-old group showing an infection rate of not less than 55 %

Surveillance was maintained from September 1963 to June, 1965 on the incidence and spread of RS virus infection in a residential nursery in the city intended for infants under 2 years of age. Two outbreaks of RS virus in

fection occurred in the nursery (III) each coinciding in time with the RS virus epidemics in the city and involving a minimum of 58 % and 83 % of the occupants respectively. During an RS virus epidemic in the city of Helsinki extending from December 1963 to about February 1964 (II) infants in 2 residential nurseries were sampled in order to discover whether they possibly had RS virus infection; the occupants in both localities were found to be heavily infected with the agent. The importance of the RS virus as a cause of respiratory disease among nursery groups of children was subsequently further evaluated in another study (VIII). Of the subjects hospitalized for diseases due to the agent, 44 % were day-nursery children, whereas among those hospitalized during the same time for infections due to respiratory pathogens other than RS virus, the proportion of children in this category was only 8 % ($p < 0.01$).

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Obtained after 1 intranasal and 2 intracardiac virus inoculations; CF titer 1/32; neutralization titer 1/2048 as determined against 10^2 TCD_{50} units of the Randall strain.

months duration and recurred at on the average, yearly intervals during the fall winter or spring. In one case the prevalence of infection extended until late June. The findings regarding the seasonal and yearly occurrence of RS virus infection are in conformity with observations from other parts of the world.

Cross neutralization tests were not performed in the present study so there is no information about the reciprocal antigenic relationship between the different epidemic strains isolated. However some of the strains were compared with each other in respect of their ability to be neutralized by Randall virus antiserum. By this means it was indirectly shown that the strains from two subsequent epidemics, that of fall 1963 and spring 1965 were antigenically distinct from each other

It can be assumed that there were high numbers of infants susceptible to RS virus at the time of the onset of the spring 1965 outbreak, since as far as is known the agent had not been prevalent in the community at all during the preceding 1 year and 3 months. Accordingly there was reason to expect a widespread dissemination of infection on this basis. As a matter of fact however certain findings seem to indicate that the spread of infection was not so extensive as expected. One is the observation that the number of admissions of very young infants with RS virus infection was comparatively small The consequences of the late onset of the outbreak in April cannot be surveyed but it appears probable that the conditions for efficient virus dissemination were not optimal at that time, and still more unfavourable during the later course of the outbreak in May and June. In view of all this, it seem possible — although direct evidence lacking — that the agent remained a tive to a limited extent somewhere the community during July and Augu until reinvolved in the well-defined ou break extending from the middle of Se tember to late November of the sam year This seems to be more plausible the inter-epidemic period was actual only about 2½ months, and the 2 strai isolated during each of the epidemi were both antigenically distinct from th Randall strain in a similar way Un fortunately both strains were not com pared directly with each other in ord to demonstrate the presence of reciproc antigenic similarities.

It was noticed that during the R virus epidemics, the agent frequently in vaded nurseries causing a high rate o infection among the occupants, and tha there was a high proportion of day nursery children among the ones who had to be hospitalized for RS virus in fection Although the reservation must be made that the social reasons for hospitalization were possibly more pressing for day nursery children than for chil dren in other categories, it would seem that RS virus infection is frequent among nursery populations. As there is, for the present a highly increasing need for more day nurseries in many urban communities due to the considerable num bers of mothers working outside the home it would seem that the importance of the agent as a cause of respiratory disease in nursery groups of children may increase further

The present study presented presumptive evidence that RS virus infection is transmitted into a family probably not

by the adult members but by the children. Moreover the results indicated a high rate of RS virus infection among the members of some families and, on the other hand, absence of infection with the agent in other families. The findings raise the question of whether there was any close association between infection in the family and infection in the nurseries, particularly the open nurseries taking care of the children during the day and sending them home in the evening. The possibility of such an association would imply the transmission of respiratory pathogens from inside the nursery to the family household unit. At present, as far as is known, there is not much knowledge about the relative importance of this means in the spread of RS virus infection.

CLINICAL FEATURES (I, II, VIII)

Material and methods

The material consisted of a total of 120 children hospitalized for acute respiratory disease associated with RS virus infection by virus isolation and/or a significant rise in CF antibody titer. Twenty-seven of the subjects were hospitalized in Turku in December 1963 and January 1964 (I), 59 during the same period in Helsinki (II) and 34 in May and June 1965 in Turku (VIII). Rhinitis and/or cough were taken to indicate an upper respiratory infection; additional rhonchi, wheezing or musical râles indicated bronchitis. Signs of breathing difficulties due to obstruction such as prolonged expiration, retraction, cyanosis and tachypnea indicated bronchiolitis; crepitant rales and/or apparen x ray evidence of infiltration of the lun parenchyma indicated pneumonia.

Results

Table 2 assembles data on all the 12 RS virus-infected children giving an indication of the relation of age to clinica syndrome. Bronchiolitis, as it was defined in the present study, was a charac teristic feature among infants of les than 1 year but was highly infrequent in the older age groups. In contras pneumonia was common up to the age of 2 years, but also occurred in the 2—<6 year-old group. As can be seen, the rate of severe lower respiratory dis-

TABLE 2. *Distribution of 120 children with respiratory syncytial virus infection according to age and clinical syndrome*

Age	Pneumonia	Bronchiolitis with pneumonia	Bronchiolitis	Bronchitis	Upper respiratory infection	Total	Severe lower respiratory disease in %
<3 mo.	4	2	2	1	—	10	90
3 mo. — <6 mo	13	10	5	3	2	33	85
6 mo. — <1 yr	16	10	3	[illegible]	4	43	72
1 yr — <2 yr	10	1	—	4	5	20	55
2 yr — <6 yr	4	—	—	5	5	14	20
Total	47	23	13	21	16	120	69

Virus isolation from throat swabs, and/or 4 fold or greater rise in CF antibody titer.
Pneumonia, bronchiolitis with pneumonia, or bronchiolitis.

case was highest in the under 3 month-old group (90 %) and showed a definite decrease with age. No fatalities occurred.

The duration of the respiratory illness and fever was approximately equal for groups of infants with RS virus infection, one (I) of which consisted of subjects < 1 year and the other (II) of subjects < years of age. The children had been ill for an average of 4 days prior to admission (II) and their illness varied in length from 7 to 21 days, being, on average, 14 (I) and 13 (II) days. The fever (higher than 37.5°C per rectum) lasted 4 days (I) or — as measured in the ward — 3 days (II) on average. The maximal duration of fever was 7 days (II). The temperature of the patients under 6 months of age never exceeded 38.1 but the temperature of those of 6 to < 12 months of age always exceeded 38.4 C per rectum (I). The percentage rates of the more severe respiratory symptoms were as follows: Dyspnoea 77 (I) and 86 (II); cyanosis 23 (I) and 22 (II); wheezing 65 (I) and 34 (II); crepitant râles 77 (I); retraction 68 (I).

Discussion

There is a striking correspondence between the present results and those achieved by McClelland *et al.* (44) in an investigation of 109 children with RS virus infection. Both studies demonstrate the high frequency with which RS virus bronchiolitis occurs in infants up to the age of 1 year and the infrequency of this clinical syndrome among children of 1 year or over. In the present series the rate of bronchiolitis and bronchiolitis with pneumonia was not less than 41 % in the under 1 year-old group but only 5 % in the 1—<2 year-old group, being 0 % in the older age groups. In contrast to the bronchiolitis syndrome, pneumonia was comparatively common up to the age of 2 years and over. This observation also corresponds to the findings of McClelland *et al.* (44).

Although a proportion of the subjects studied were admitted for social and otological (otitis media) reasons, the majority were considered to be in need of hospital care for their severe lower respiratory disease and were hospitalized on these grounds. The present material of 120 children thus represents, to a considerable extent, a selection of the severest cases of RS virus infection. It can be emphasized that the results hence do not give any direct indication of the rate of severe lower respiratory disease caused by the agent among the open pediatric population of the city.

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TABLE 3. *Rate of respiratory syncytial (RS) virus isolations from middle ear aspirates of 28 children with RS virus infection*

Epidemic	No. children yielding virus from one or both ears / No. children punctured	No. ears yielding virus / No. ears punctured
Spring 1963	9/10 (90 %)	13/17 (76 %)
Fall 1963	7/18 (39 %)	11/34 (32 %)
Total	16/28 (57 %)	24/51 (47 %)

RS virus isolation from throat swabs.

containing exudates were sometimes thin and sanguinous.

Virus was recovered during the fall study with about equal frequency from ears with injected, reddened and/or bulging eardrums (isolation rate 30 %) and ears lacking these signs of inflammation (isolation rate 35 %). One child whose eardrums were reddened and dull and who did not receive treatment with antibiotics at the time of the puncture yielded RS virus and *Haemophilus influenzae* from both ears (XI).

The aspirates which yielded virus were obtained from the 3rd to 9th day after the onset of the respiratory symptoms (IV, V, XI). Only 1 of the aspirates obtained at repuncture contained virus. In this case the time interval between the two positive exudate specimens was 4 days (XI). Only 1 of the children studied was with certainty known to be suffering from RS virus reinfection. The aspirates of this boy obtained 7 days after the onset of respiratory symptoms were negative for virus (XI).

As previously indicated (IV), cultures were simultaneously inoculated with throat swabs and aspirate specimens. The time required for the CPE to become apparent varied greatly but was in general shorter for the swab-inoculated cultures than for the cultures inoculated with aspirates. It never occurred that RS virus was recovered from middle ear aspirates, but not recovered from the throat swabs taken at the same time from the same subject. On the contrary it often happened that the aspirates were negative, but the throat swabs yielded virus, especially in the later course of the disease.

Discussion

Although it is not known whether RS virus is capable of multiplying in the human middle ear epithelium, the accumulation of RS virus-containing mucus in the tympanum seems to justify the use of the term *RS virus otitis*. The affection can be detected by a careful examination of the eardrums. The spring study (IV, V) convincingly demonstrated its clinically weak manifestations. None of the 9 infants suffering from RS virus otitis developed any signs of more

OTOLOGY (IV, V, VI)

Material and methods

The patients were young children who were admitted to the wards of the Children's Clinic of the University or the Hospital for Infectious Diseases in Helsinki, or were seen in the outpatient department of the Otolaryngological Clinic of the University. All patients took part in the study during the RS virus outbreaks in spring 1965 (IV, V) and fall 1965 (VI). RS virus was isolated from the throat swabs of a total of 28 children. The ages of these 28 subjects who were suffering from RS virus infection and who will be considered otologically in greater detail in this report were as follows:

Epidemic	Age in months	Inpatients	Outpatients
Spring 1965	12	9	
	21		1
Fall 1965	<12	16	
	12	1	
	38		1
	Total	26	2

Middle ear exudate specimens were obtained with a syringe and needle by a puncture aspiration technique and the aspirates withdrawn were immediately inoculated undiluted through the needle into a HeLa cell culture tube. The ear drums of each child were punctured once or more times during the course of the respiratory illness. Because only the first later results than the first punctures will be discussed and recorded in the tables. Not less than 18 (64%) of the 28 subjects were treated with antibiotics at the time of the puncture.

Results

RS virus was isolated from the middle ear aspirates of 16 (57%) of the children or from 21 (75%) of the ears punctured. However, as shown in Table 1 the isolation rate varied from time to time, being higher in the spring than in the fall. Of the 10 children in the spring series, 9 (all of whom were ≤12 months old) had isolation positive and 1 (21 months old) isolation negative aspirates. Of the 18 children of the fall series only 7 (6 of whom were ≤12 and one 38 months old) had isolation positive aspirates.

All children included in the spring study (IV, V) displayed signs of a very weak middle ear affection. The eardrum was pale, dull or lustreless, thin or slightly thick and in normal position, the light and with the reflex visible or invisible. The RS virus containing exudates obtained from these cases were clear and mucous and did not contain pathogenic bacteria. In contrast, a considerable proportion of the children in the fall study (VI) displayed signs of a more acute middle ear inflammation. Their virus

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The aspirates which yielded virus were obtained from the 3rd to 9th day after the onset of the respiratory symptoms (IV, V, XI). Only 1 of the aspirates obtained at repuncture contained virus. In this case the time interval between the two positive exudate specimens was 4 days (XI). Only 1 of the children studied was with certainty known to be suffering from RS virus reinfection. The aspirates of this boy obtained 7 days after the onset of respiratory symptoms were negative for virus (XI).

As previously indicated (IV), cultures were simultaneously inoculated with throat swabs and aspirate specimens. The time required for the CPE to become apparent varied greatly but was in general shorter for the swab-inoculated cultures than for the cultures inoculated with aspirates. It never occurred that RS virus was recovered from middle ear aspirates, but not recovered from the throat swabs taken at the same time from the same subject. On the contrary it often happened that the aspirates were negative, but the throat swabs yielded virus, especially in the later course of the disease.

Discussion

Although it is not known whether RS virus is capable of multiplying in the human middle ear epithelium, the accumulation of RS virus-containing mucus in the tympanum seems to justify the use of the term RS virus otitis. The affection can be detected by a careful examination of the eardrums. The spring study (IV, V) convincingly demonstrated its clinically weak manifestations. None of the 9 infants suffering from RS virus otitis developed any signs of more

OTOLOGY (IV V, XI)

Material and methods

The patients were young children who were admitted to the wards of the Children s Clinic of the University or the *Hospital for Infectious Diseases* in Turku or were seen in the out patient department of the Otolaryngological Clinic of the University All patients took part in the study during the RS virus out breaks in spring 1965 (IV V) and fall 1965 (XI) RS virus was isolated from the throat swabs of a total of 28 children. The ages of these 28 subjects who were suffering from RS virus infection, and who will be considered otologically in greater detail in this report where as follows

Epidemic	Age in months	Inpatients	Out patients
Spring 1965	≦1	9	—
	1	—	1
Fall 1965	<12	16	—
	22	1	—
	38	—	1
	Total	26	2

Middle ear exudate specimens were obtained with a syringe and needle by a puncture aspiration technique and the aspirates withdrawn were immediately inoculated undiluted through the needle into a U cell culture tube. *One or* both ears of each child were punctured one or more times during the course of the respiratory disease only the isolation results from the first puncture will be discussed and recorded in the table. Not less than 26 (93 %) of the 28 subjects were treated with antibiotics at the time of the puncture.

Results

RS virus was isolated from the middle ear aspirates of 16 (57 %) of the children or from 24 (47 %) of the ears punctured. However as shown in Table 3, the isolation rates varied from time to time being higher in the spring than in the fall Of the 10 children in the spring series, 9 (all of whom were ≦12 months old) had isolation positive and 1 (21 months old) isolation negative aspirates. Of the 18 children of the fall series, only 7 (5 of whom were <12, one 22 and one 38 months old) had isolation positive aspirates.

All children included in the spring study (IV V) displayed signs of a very weak middle ear affection The eardrum was pale, dull or lustrous, thin or slightly thickened, in normal position, rigid and with the reflex visible or invisible. The RS virus-containing exudates obtained from these ears were clear and mucous or serous, and did not contain pathogenic bacteria In contrast, a considerable proportion of the children in the fall study (XI) displayed signs of a more severe middle ear inflammation their virus-

TABLE 3. *Rate of respiratory syncytial (RS) virus isolations from middle ear aspirates of 28 children with RS virus infection*

Epidemic	No. children yielding virus from one or both ears / No. children punctured	No. ears yielding virus / No. ears punctured
Spring 1963	9/10 (90 %)	13/17 ([illegible] %)
Fall 1963	7/18 (39 %)	11/34 (32 %)
Total	16/28 (57 %)	24/51 (47 %)

RS virus isolation from throat swabs.

containing exudates were sometimes thin and sanguinous.

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cumulation and a rigid eardrum in young infants with narrow external acoustic meatus. The advantages of the puncture aspiration technique and the direct inoculation technique used in the present study can not be evaluated in greater detail since alternative methods were not employed.

severe inflammation such as redness or injection of the eardrum. As a matter of fact only rigidity of the drum was common to all of the children as revealed by the use of Siegle's pneumatic speculum and probably mainly attributable to intratympanic mucus accumulation. The fact that RS virus otitis may heal without the development of more pronounced signs of inflammation seems to indicate that the affection is comparatively harmless and probably without clinical significance provided the occurrence of complicating bacterial otitis media can be avoided

If uncomplicated RS virus otitis were associated with redness, injection or bulging of the drums, one would expect to find these signs regularly in infants infected with the agent This, however is not the case Out of 13 infants suffering from RS virus pneumonia in a nursery in the U.S.A., 7 (50 %) had reddened tympanic membranes (39) but among 15 RS virus-infected infants in another nursery in Stockholm Sweden there was no evidence at all of this feature (56) According to other reports, *RS virus infection may be associated* with definite signs of otitis media in 8 to 32 % of the cases (35 46 49 58) It would seem that the variations in the occurrence of eardrum signs in association with respiratory illness due to RS virus, can only be explained on the basis of variations in the rates of complicating bacterial middle ear inflammation It seems clear that the risk of an extensive spread of bacterial respiratory pathogens is increased during RS virus outbreaks, particularly in institutions providing care for infants, and that concomitant bacterial middle ear infection may thus be a common occurrence in a number of young RS virus-infected children, if not prevented by prophylactic treatment with antibiotics or other measures. It is not known to what extent and by what mechanism RS virus otitis lowers the resistance of the middle ear to superinfection but it is possible that the presumptive destruction of the epithelium may help bacterial pathogens to penetrate it and invade the submucosal space It appears likely that lack of aeration and drainage may be one, if not the most important factor contributing to the aggravation of the symptoms of bacterial inflammation.

Successful isolation of RS virus from the middle ear is facilitated by early puncture. On no occasion was the agent recovered later than the 9th day after the onset of the respiratory disease. Under favourable conditions the agent can be recovered from the ears of 100 % of the infants of 12 months or younger (IV V) Only a few older children were sampled so there is no data available on the chances of a positive isolation from the aspirates of subjects of over 1 year of age. The results indicate simply that virus-positive aspirates can be obtained up to the age of at least 3 years (XI) It is worthy of note that exudates from ears with simultaneous bacterial middle ear inflammation were also capable of yielding virus. It was desirable or important to change the inoculated cultures to fresh medium as soon as possible after the virus adsorption in order to diminish the occasionally toxic effect of the exudate on the cell culture A useful requisite was a new model of Siegle's pneumatic speculum specially designed to demonstrate intratympanic mucus ac-

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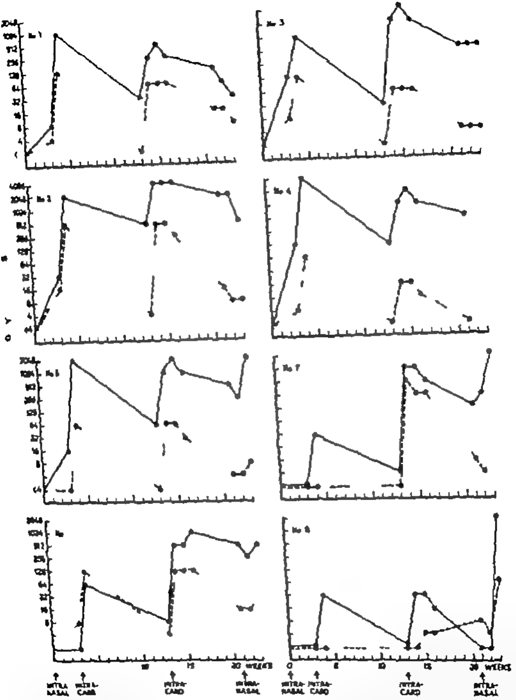

Fig 1 An ibody response f guinea pigs to intranasal and intracardiac inoculations of respiratory syncytial irus. Inoculations are indicated by arrows. Points connected by solid lines indicate neutralizing antibody titers; points connected by dotted lines complement f xing antibod ters.

EXPERIMENTAL (VI, VII, X)

Material and methods

The study of the susceptibility of the middle ear of the guinea pig to RS virus (VI VII) included 6 experiments in which the ears of a total of 34 animals were inoculated with virus, and the ears of 7 animals with control fluid from uninoculated tissue cultures. Two strains of virus were used The Randall and the Lamminpää strains. The latter strain had been isolated in the spring 1965 from a middle ear aspirate of a child with RS virus otitis. The inoculation technique was as follows About 0 1 ml virus suspension or control fluid was injected through the eardrum using a needle and syringe. The animals were killed after 5 7 or 14 days the middle ear cleft entered through the temporal bone and specimens obtained from the middle ear for the isolation of virus and bacteria. The virus isolation specimens were obtained either with a platinum loop by removing small pieces of the mucosa or by washing the cleft After sampling the temporal bone with its accompanying middle ear was removed for histological examinations. A considerable number of the animals suffered from natural chronic bacterial otitis media

In the study of the immune response of guinea pigs to intranasal and intracardiac RS virus inoculations (X) 8 guinea pigs were inoculated with virus (Strain Randall) and 3 with control fluids from uninoculated tissue cultures. The virus used for intranasal instillations was grown in U cells, and the virus used for intracardiac injections in primary guinea pig kidney tissue cultures. Serum specimens were examined for neutralizing and CF antibody and for precipitating antibody using an agar gel diffusion technique.

Results

Virus was isolated from the middle ear cavity of the animals 5 and 7 days post inoculation (VI VII) all the specimens obtained 14 days post inoculation were negative for virus. The washing method was superior to the one in which the virus was isolated from mucosal pieces. With the washing method the agent was recovered from 25 % of the isolation specimens obtained but with the latter method from only 7 %. The agent was recovered proportionally more frequently in ears free from bacterial inflammation than from ears naturally infected with bacteria. With the washing technique RS virus was isolated from 47 % of the ears in the former category but from only 13 % of the ears in the latter category Similar isolation rates were noticed for the both virus strains used in the experiments.

Histological examination of the ears with no bacterial inflammation yielded

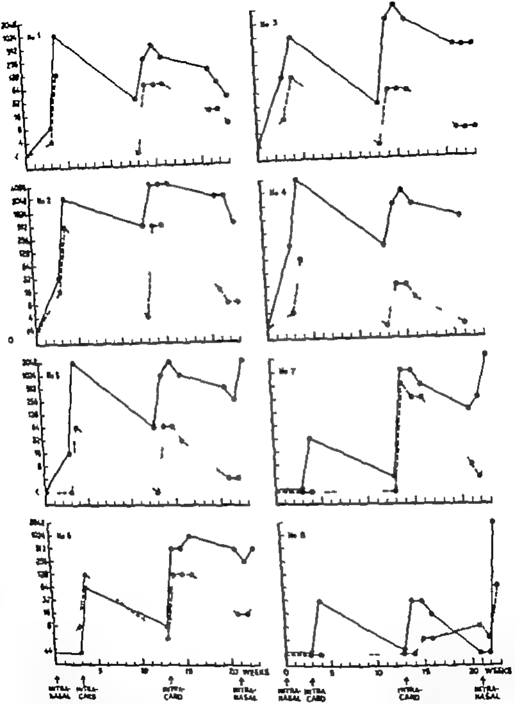

Fig. 1 — Antibody response of guinea pigs to intranasal and intracardiac inoculations of respiratory syncytial virus. Inoculations are indicated by arrows. Points connected by solid lines indicate neutralizing antibody titers; points connected by dotted lines, complement fixing antibody titers.

the following results (VI VII) A weak inflammation of subacute type was noticed in 77 % of the virus inoculated ears from which virus was recovered in 70 % of the virus-inoculated ears from which virus was not recovered and in none of the ears (only 8 in number) inoculated with control fluid The subacute inflammation typical of the virus-inoculated ears was characterized by edema proliferation of the connective tissue and infiltration predominantly with lymphocytes, histiocytes and macrophages. In 3 ears, multinucleated giant cells were seen in the exudate on the surface of the epithelial lining of the bulla. Out of 26 animals none showed antibody 5 or 7 days after the virus inoculation but on the 14th day a low level RS virus antibody response was noticed in 2 animals out of 8

The immune response of the guinea pig to RS virus inoculations was evaluated in greater detail in study No X. Figure 1 shows the neutralizing and CF antibody responses of the 8 guinea pigs receiving intranasal and intracardiac inoculations of virus. As can be seen, the extent of antibody formation after the 2 intranasal inoculations varied greatly the 2 intracardiac inoculations were followed by a more uniform antibody formation. None of the virus-inoculated or 3 control animals showed CF antibody against the antigens present in the U cell cultures none of the control animals developed antibody against RS virus.

A maximum of 3 different virus-specific precipitation lines were detected (X) The lines were marked *a*, *b* and *c*. The *a* line was situated nearest to the antigen well. The *b* line was mostly situated half way between the antigen and the serum well, and it was often duplicated. The *c* line was always ad

TABLE 4 *Precipitating antibody response in guinea pigs to intranasal and intracardiac inoculations of respiratory syncytial virus.*

Animal no.	Time in weeks									
	0	3	4	13	14	13	16	1	22	23
1	—	*b*	*b*	*b*	*abc*	*b*	*b*	*b*	*bc*	*abc*
2	—	—	*b*	*b*	*bc*	*abc*	*bc*	*bc*	*bc*	*bc*
3	—	—	*ab*	—	*b*	*b*	*b*	*b*	*b*	*b*
4	—	—	*b*	—	*b*	*b*	*b*	*b*		
5	—	—	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*ab*
6	—	—	*b*	*b*	*ab*	*ab*	*ab*	*b*	*ab*	*abc*
7	—	—	—	*b*	*b*	*b*	*b*	*b*	*b*	*b*
8	—	—	—	—	*b*	*b*	*b*	*b*	*b*	*bc*

Differe t precipitation lines are designated with *b* and *c*.

Intranasal inoculations w re given t 0 and 21 weeks.

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Discussion

The question of whether the RS virus was reproducing or was being simply mechanically preserved in the middle ear of the guinea pigs could not be solved conclusively in the present study since tissue homogenates of the mucosa were not prepared, and no titrations carried out to demonstrate a rise in the infectivity titer of the agent in this tissue, nor were other methods used to directly demonstrate the presence of the agent in the mucosal cells of the middle ear. However, the study provided indirect presumptive evidence that virus reproduction was taking place in the middle ear of the animals: 1) The agent was recovered 7 days post inoculation from the ears of a considerable number of the animals. Since RS virus loses its infectivity comparatively rapidly at temperatures around those of the guinea pig middle ear, it is not likely that it would have lived through the period from inoculation to sampling without reproducing. 2) The inflammatory reaction of the ears inoculated with virus as compared to the apparently normal histological picture of the ears which were inoculated with control fluid. 3) The presence of multinucleated giant cells probably of epithelial origin in the exudate on the epithelial lining of some of the virus-inoculated ears.

Two advantages of the method of preparing hyperimmune guinea pig RS virus antiserum by giving the animals a combination of 1 intranasal and 2 intracardiac inoculations, were the high titered specific neutralizing, CF and precipitating antibody formation even after the first booster and the absence of host (tissue culture) antibody response. It was necessary to give 2 boosters, since the precipitin response was more complete after the second one than after the first.

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3	—	—	ab	—	b	b	b	b	b	b
4	—	—	b	—	b	b	b	[illegible]		
5	—	—	b	b	ab	ab	b	ab	ab	b
6	—	—	b	b	b	b	ab	b	ab	abc
7	—	—	—	b	b	b	b	b	bc	b
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SUMMARY

1. The method of inoculating sensitive tissue cultures directly with applicators containing throat secretions proved useful for the isolation of RS virus. A continuous line of human amnion (U cells) proved more suitable than the BS-C1 cells. The mean time required for the CPE to become apparent was 6 days for the former type of culture and 13 days for the latter. Eighty % of the positive U cultures showed a definite CPE within 1 week following inoculation. The likelihood of detecting RS virus infection in children under 6 years of age by the direct inoculation technique using U cells was higher during the first week of illness (82 % positive specimens) than in the second (49 % positive specimens), third (21 % positive specimens) and fourth weeks (11 % positive specimens). Two throat swabs, each immersed in a separate tissue culture tube, proved sufficient for the isolation of the virus at the acute stage, but during the later course of the disease it was desirable to inoculate more than 2 tubes. RS virus was isolated from 64 % of children with bronchiolitis, 60 % with pneumonia, 21 % with bronchitis and 13 % with upper respiratory infection. The proportion of children positive by isolation decreased with age. Not less than 70 % of the under 3 month-old subjects with respiratory infection yielded the agent. In order to improve the chances of a positive serodiagnosis by the CF technique in children under 3 months of age it was found necessary to initiate the titration from a serum dilution of 1/4 or lower and to employ a convalescent serum which was not obtained before the 5th week of illness. Seven adults with RS virus infection did not develop CF titers of higher than 1/16. Findings suggested that besides age previous experience with RS virus may also be a factor determining the concentration of viral antigen required in the CF test. A comparison of the isolation method (using the direct inoculation technique and U cells) and the CF test revealed the following results. The isolation method was highly efficient in detecting infection in subjects under 5 years (efficiency 86—100 %), the CF test in subjects of 1 year or over (efficiency 100 %).

2. Four fairly sharply limited outbreaks of RS virus infection, each of about 3 months duration, occurred in the city of Turku during the period September 1963 to December 1966. The inter-epidemic periods varied in length from 3 months to 1 year and 2 months. The virus strain involved in the fall 1963 outbreak was found to be antigenically distinct from the one involved in the next outbreak in the spring 1965. During these two outbreaks there was a different distribution according to the age of the children who had to be hospitalized for RS virus infection. The

fall, 1963 series was made up of proportionally many very young infants, the spring, 1965 series of a greater proportion of older children. In one of the series (spring, 1965) the proportion of day nursery children among those having RS virus infection was not less than 44 Two outbreaks of RS virus infection in a residential nursery coincided with epidemics involving the whole city The agent also invaded nurseries in the city of Helsinki during an epidemic occurring there. RS virus infection was found to spread easily among family members, particularly among children but also to some degree among parents. Serological data suggested that the infection was brought into the families by the children.

3. A hundred and twenty children hospitalized for RS virus infection were divided into different disease categories according to age Bronchiolitis was a characteristic feature of the under 1 year old infants, but was highly infrequent among those of 1 year or over In contrast pneumonia was common up to the age of [illegible] years, but also occurred, to some degree among those of [illegible] years or over The rate of severe lower respiratory disease was highest in the under 3 month old group (90 [illegible]) and showed a decrease with age

4 Middle ear exudate specimens were obtained by puncture aspiration through the eardrum and the aspirates withdrawn immediately inoculated undiluted into [illegible] cell cultures RS virus was isolated from the throat swabs of 38 children and a positive virus isolation obtained from the aspirates of 16 (37 %) of these subjects or from 4 (47 %) of the ears punctured A higher proportion of RS virus-infected children yielded RS virus from their ears during the spring, 1965 (90 %) than during the fall 1965 outbreak (30 %) The majority of the children punctured and yielding virus were under 12 months. The oldest subject from whom a positive isolation was obtained from an aspirate was 38 months, and the youngest [illegible] months. In a considerable proportion of the cases, RS virus otitis appeared and healed without the development of redness, injection or bulging of the drum, but in other cases these signs were apparent. Since almost all the subjects were treated with antibiotics, specimens for the isolation of bacteria were not systematically obtained. One ear yielded virus twice at an interval of 4 days. The aspirates of 1 child with reddened eardrums contained both *Haemophilus influenzae* and RS virus. This child was not being treated with antibiotics. In a case of proved reinfection the aspirates were negative for virus. The agent was never isolated later than the 9th day after the onset of respiratory symptoms, although the throat swabs yielded virus continually

5. *Thirty four guinea pigs were inoculated with RS* virus via the eardrum, and 7 with control fluid. A proportion of the animals suffered from natural chronic bacterial otitis media. The agent was isolated from the middle ear cavity 3 and 7 days post inoculation. About 4 times as many positive isolations were obtained by washing the middle ear as by another method in which the isolation specimens consisted of mucosal pieces. The agent was recovered 1 week after inoculation from 4[illegible] % of the ears free from bacterial inflammation, but from only 13 % of the ears naturally infected

SUMMARY

1. The method of inoculating sensitive tissue cultures directly with applicators containing throat secretions proved useful for the isolation of RS virus. A continuous line of human amnion (U cells) proved more suitable than the BS-C1 cells. The mean time required for the CPE to become apparent was [illegible] days for the former type of culture and 13 days for the latter. Eighty % of the positive U cultures showed a definite CPE within 1 week following inoculation. The likelihood of detecting RS virus infection in children under 6 years of age by the direct inoculation technique using U cells was higher during the first week of illness (62 % positive specimens) than in the second (49 % positive specimens), third (21 % positive specimens) and fourth weeks (11 % positive specimens). Two throat swabs, each immersed in a separate tissue culture tube, proved sufficient for the isolation of the virus at the acute stage, but during the later course of the disease it was desirable to inoculate more than 2 tubes. RS virus was isolated from 64 % of children with bronchiolitis, 50 % with pneumonia, 21 % with bronchitis and 13 % with upper respiratory infection. The proportion of children positive by isolation decreased with age. Not less than 70 % of the under 3 month-old subjects with respiratory infection yielded the agent. In order to improve the chances of a positive serodiagnosis by the CF technique in children under 3 months of age it was found necessary to initiate the titration from a serum dilution of 1/4 or lower and to employ a convalescent serum which was not obtained before the 5th week of illness. Seven adults with RS virus infection did not develop CF titers of higher than 1/16. Findings suggested that besides age previous experience with RS virus may also be a factor determining the concentration of viral antigen required in the CF test. A comparison of the isolation method (using the direct inoculation technique and U cells) and the CF test revealed the following results: The isolation method was highly efficient in detecting infection in subjects under 5 years (efficiency 86—100 %), the CF test in subjects of 1 year or over (efficiency 100 %).

2. Four fairly sharply limited outbreaks of RS virus infection, each of about 3 months duration, occurred in the city of Turku during the period September 1963 to December 1966. The inter-epidemic periods varied in length from 3 months to 1 year and 2 months. The virus strain involved in the fall 1963 outbreak was found to be antigenically distinct from the one involved in the next outbreak in the spring 1965. During these two outbreaks there was a different distribution according to the age of the children who had to be hospitalized for RS virus infection. The

fall, 1963 series was made up of proportionally many very young infants, the spring, 1965 series of a greater proportion of older children. In one of the series (spring, 1965) the proportion of day-nursery children among those having RS virus infection was not less than 44 %. Two outbreaks of RS virus infection in a residential nursery coincided with epidemics involving the whole city. The agent also invaded nurseries in the city of Helsinki during an epidemic occurring there. RS virus infection was found to spread easily among family members, particularly among children, but also to some degree among parents. Serological data suggested that the infection was brought into the families by the children.

3. A hundred and twenty children hospitalized for RS virus infection were divided into different disease categories according to age. Bronchiolitis was a characteristic feature of the under 1 year old infants, but was highly infrequent among those of 1 year or over. In contrast, pneumonia was common up to the age of years, but also occurred, to some degree, among those of years or more. The rate of severe lower respiratory disease was highest in the under 3 month-old group (%) and showed a decrease with age.

4. Middle ear exudate specimens were obtained by puncture aspiration through the eardrum and the aspirates were drawn immediately inoculated undiluted into cell cultures. RS virus was isolated from the throat swabs of 25 children, and a positive virus isolation obtained from the aspirates of 16 (37 %) of these subjects, or from 4 (47 %) of the ears punctured. A higher proportion of RS virus-infected children yielded RS virus from their ears during the spring, 1965 (90 %) than during the fall, 1965 outbreak (30 %). The majority of the children punctured and yielding virus were under 12 months. The oldest subject from whom a positive isolation was obtained from an aspirate was 38 months, and the youngest ? months. In a considerable proportion of the cases, RS virus otitis appeared and healed without the development of redness, injection or bulging of the drum, but in other cases these signs were apparent. Since almost all the subjects were treated with antibiotics, specimens for the isolation of bacteria were not systematically obtained. One ear yielded virus twice at an interval of 4 days. The aspirates of 1 child with reddened eardrums contained both *Haemophilus influenzae* and RS virus. This child was not being treated with antibiotics. In a case of proved reinfection the aspirates were negative for virus. The agent was never isolated later than the 9th day after the onset of respiratory symptoms, although the throat swabs yielded virus continually.

5. Thirty four guinea pigs were inoculated with RS virus via the eardrum, and 7 with control fluid. A proportion of the animals suffered from natural chronic bacterial otitis media. The agent was isolated from the middle ear cavity 5 and 7 days post inoculation. About 4 times as many positive isolations were obtained by washing the middle ear as by another method in which the isolation specimens consisted of mucosal pieces. The agent was recovered 1 week after inoculation from 47 % of the ears free from bacterial inflammation but from only 13 % of the ears naturally infected

with bacteria. Histological examination of the ears with no bacterial inflammation revealed the following results A weak subacute inflammation was noticed in 77 % of the virus-inoculated ears from which virus was recovered in 70 % of the virus-inoculated ears from which virus was not recovered and in none of the ears (only 8 in number) inoculated with control fluid. Three virus-inoculated ears showed multinucleated giant cells probably of epithelial origin.

Eight guinea pigs received intranasal and intracardiac inoculations of virus, and 3 guinea pigs similar inoculations of control fluid. The specific immune responses noticed were more uniform after the intracardiac injections. In addition to the neutralizing and CF antibodies to RS virus the animals also developed specific precipitating antibodies of 3 types. To induce a complete precipitin response it was necessary to give not less than 1 intranasal and ? intracardiac inoculations.

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The study was carried out at the Department of Virology University of Turku and in part at the Hospital for Infectious Diseases in Turku, the Otolaryngological Clinic the Departments of Medical Microbiology and Pathological Anatomy and the Children's Clinic, University of Turku, and at the Epidemic and Medical Department for Children, Aurora Hospital, Helsinki. I wish to thank the personnel of those institutions for their courtesy and assistance. I wish to thank, in particular Miss Anja Pajasmaa for her assistance in the serological tests, Mrs. Leena Soini for preparing the tissue cultures, Mrs. Tuulikki Ström for collecting samples and necessary information, and Mrs. Maija Aro for her secreterial assistance.

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VECTORCARDIOGRAPHIC STUDIES IN NEWBORN INFANTS

BY PENTTI HÄNNINEN

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FROM THE CHILDREN'S HOSPITAL
(HEAD PROF TOOMAS PELTONEN, M D) AND THE CARDIORESPIRATORY RESEARCH UNIT
(HEAD ASSOC. PROF LEO HIRVONEN, M D) OF TURKU UNIVERSITY TURKU FINLAND

Vectorcardiographic Studies in Newborn Infants

BY
PENTTI HANNINEN

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PREFACE

The late Professor Toivo Salmi, earlier my teacher and chief, began the series of neonatal cardiologic studies in Turku with which my work is connected. I remember him with sincere gratitude. His sympathetic and friendly attitude were invaluable when I started on this work in his department.

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My thanks are also due to Dr Kaarlo Hartiala, M.D. Professor of Physiology Head of the Department of Physiology of Turku University in which the Cardiorespiratory Research Unit is located.

I am very grateful to Dr Ole Wasz-Hockert, M.D. Professor of Pediatrics, Head of the Department of Pediatrics of University of Oulu, my former chief for allowing me to supplement my material in his department and for helping me in many ways.

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Mr Heikki Alikoski, Phil.lic., was my advisor on the statistical aspects of the work. I am grateful to him for his interest and co-operation. Mr Erkki Hänninen, my younger brother performed all the mathemathical calculations with commendable care.

In the recordings, I received great help from the members of the staffs of the Children's Hospital of Turku University the Department of Pediatrics of University of Oulu, Abolands Sjukhus hospital and the Cardiorespiratory Research Unit of Turku University. My work would haven been much more difficult without the help that I was accorded by all of them.

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Turku, May 1967

Pentti Hänninen

INTRODUCTION

Electrocardiography has long been an important method of cardiac study. Vectorelectrocardiography or vectorcardiography (Vcg) has made a significant contribution to the application of electrocardiography. It complements the sum of knowledge obtainable on the electrical activity of the heart. Vectorcardiographic research has its own specific spheres, whereas certain other areas of the electrical activity of the heart are displayed better by ordinary electrocardiography. It is in fact customary in many cardiac research centres to make both Ecg and Vcg recordings when studying on the surface of the skin the electrical potentials generated by the heart.

The vectorcardiographic method has been little used for newborn. But as e.g. the ratio between the action potentials of the different halves of the heart is revealed better by Vcg than by ordinary Ecg, and as this ratio is particularly difficult to assess in the newborn and is of diagnostic significance, vectorcardiography could be expected to be of great value in studying the electrical activity of the heart of the newborn. Furthermore, it is sometimes difficult, in the neonatal period in particular, to diagnose partial bundle branch blocks, which also is one of the »specialities» of vectorcardiography.

The use of the vectorcardiographic method in cardiology of the newborn seems, thus, to be very well motivated. Its application to the newborn, however, raises problems which are not encountered to the same extent in older children or adults. This may be the reason why there are *so few studies dealing with the newborn*.

The rapid progress in the facilities for treating many severe conditions of congenital heart disease operatively and at earlier ages makes it essential to improve early diagnostics. To establish firm grounds for vectorcardiographic diagnosis, we must try to ascertain from a sufficiently large material what the normal findings and dispersions are for healthy newborn infants. We must also establish which recording methods are applicable for examination of the newborn. More accurate and more reliable determination of the electrical potentials of the heart should also throw further light on the normal hemodynamics of the neonatal period.

The purpose of the present study is, within the above frame of reference, to examine the potential and technique of the vectorcardiographic method in the neonatal period and to present the normal findings.

HISTORY OF VECTORCARDIOGRAPHIC RESEARCH

The observation by Einthoven in 1913 that the waves of the scalar electrocardiogram are projections on certain axes of an imaginary heart vector which illustrates the changing electrical status of the heart is the basis of both ordinary electrocardiography and vectorcardiography [51] Einthoven was not the first to record the electrical action of the heart. Waller had made graphic recordings of the electric current generated by the human heart as early as 1887 [226]

The vectorial mode of thinking evolved by Einthoven was soon applied to electrocardiographic analysis by other workers who used it to elucidate the Ecg changes of bundle branch blocks, hypertrophies and auricular flutter [136, 235] In 1920 Mann constructed vectorcardiographic loops from an ordinary Ecg and called them monocardiograms [140]

Although these earlier studies were conducted only on the frontal plane they created a basis for the theory of the electric dipole of the heart, which has since been explained by Craib [37] who introduced the term dipole and which has become one of the fundamental ideas in the study of the electrical action of the heart. It has been claimed that Einthoven's research team was already aware of spatial vector implications, although they did not postulate them. Possibly they feared that this would make the new method of investigation look too complicated [212]

Savjaloff drew attention in 1929 to the three dimensional character of the potentials generated by the heart. He noted that in recordings made on the frontal plane only the differences of potentials emerge which are parallel to the frontal plane He denoted the spatial potential difference E^{st} its projection on the frontal plane E_a and the angle which the spatial potential difference formed with the frontal plane S This gives $E_a = E^{st} \cos S$ Consequently not much can be known about the spatial differences in potential without knowing the angle S [195]

The spatiality of potentials was studied systematically by Wilson, who placed electrodes on different parts of the trunk and determined the sagittal component between the electrodes placed before and after the heart [236]

Direct recording of vectorcardiographic (Vcg) loops became possible in 1930 when Mann announced that he had already devised in 1925 an apparatus capable of direct recording of monocardiograms, as he called them [141] He used this device for studying heart function in normal and pathologic conditions and considered that the method was very suitable for diagnosis of right and left bundle branch

blocks and helpful in the study of problems such as the site and extent of myocardial and coronary lesions, the nature of fibrillation and flutter and the sites of origin of extrasystoles. In 1938 Mann devised a new electromechanical oscillograph [142]

The cathode-ray tube, introduced in the early 1930s, made it possible to perform Vcg recordings more easily and with greater sensitivity It ushered in a new phase of development in the history of vectorcardiography The cathode-ray tube was employed in Vcg recording by two research teams almost simultaneously in 1937 and practically independently of one another viz. Schellong et al. [202] and Wilson et al. [238]

In 1937 Schellong *et al.* published three studies on Vektordiagraphie for which they used the abbreviation VD [202, 203, 204] The first paper dealt with the bases of the new technique. The second described its practical application in the differential diagnosis of conduction defects, on the one hand, and innocent notches and fragmentations on the other The third paper was a discussion of the practical method and the normal findings. Schellong had already described the method a year earlier at the Wiesbaden Congress.

It is surprising how clearly investigators were able to establish even at that time the most important characteristics of a normal Vcg finding. Many observations made by Schellong's team are still valid. For instance they found the QRS loop to be at roughly the same plane which they called »die Ebene der QRS-Schleife The configuration and spatial orientation of normal QRS and T loops were presented, likewise the concordance of QRS and T loops. Examples of normal recordings were presented. The normal QRS loop was described as having the following features.

1. dass sie in einer Hauptebene verläuft, wobei der Q-Teil und der absteigende Teil von R nach vorn, der aufsteigende Teil von R und der S-Teil nach hinten zu gelegen sind,

2. dass die QRS-Schleife eine ellipsenähnliche Form hat, die zwar in manchen Fällen durch flache Ein- und Ausbuchtungen unterbrochen werden kann, welche aber nicht aus der allgemeinen Ebene herausfallen.

The authors also suggested the possibility of using limb leads in Vcg recording. However they thought that the results obtained in this way were so inconsistent that the characteristics of a normal finding could not be established.

In 1938 Schellong reported a method of direct recording stereoscopically by moving the dorsal electrode. The two pictures obtained were then viewed stereoscopically [200]

In 1937 Hollman and Hollman also used the cathode-ray tube, using a slight modification of Schellong's example for recording vector loops [99 100] They called these triograms.

Wilson spoke on the use of the cathode-ray tube for the first time in May 1937 at the American Society for Clinical Investigation, and later in the same year in collaboration with Johnston and Barker published a written paper on it [238] He employed

in it his tetrahedron system which is still in use today

Vcg findings in left and right axis deviations and in bundle branch blocks were studied a year later by Wilson and Johnston, who also reported a case with infarction of the diaphragmatic wall of the heart. The recordings were performed in the frontal plane and time integration was included by using a broken line. These authors suggested the name vector cardiogram. The curves obtained by this method are vector functions of the time and may be called vector cardiograms. [237]

An orthogonal system which differs very little from that employed by Schellong was used in 1939 by Kimura in his recordings [116] He also discussed points of a fundamental character Kimura was influenced by Schellong, whose name is mentioned in his publication.

In 1939 Schellong wrote a comprehensive study entitled Grundzüge einer klinischen Vektordiagraphie des Herzens [201] The construction of Vcgs from scalar curves and vice versa were both described, and also the technique of Vcg recording using the Siemens-Vektordiagraph. Normal findings for different positions of the heart and the most important pathologic signs were reported. But time integration was omitted since it was not possible with this apparatus to record the loop as a broken line. The most important Vcg alterations in connection with myocardial infarctions were also described.

Once a beginning had thus been made in vectorcardiography by means of the cathode-ray tube the technique was developed rapidly Very thorough and versatile work was done in the 1940s and especially in the 1950s to clarify the theory of vectorcardiography and to evolve new and more reliable recording methods, as will be related later in this review of the literature It became customary to make the recordings in three planes to give an accurate spatial representation, and the express aim in analysing the results was determination of the quantitative facts. Many new methods of analysing and presenting the results were introduced. The literature in this field has now assumed voluminous proportions.

RECORDING SYSTEMS

When the action potentials produced by the heart are recorded from the skin there are naturally an unlimited number of alternatives for placing the electrodes. In addition, the impulses received via the electrodes can be treated in different ways. The simplest method is to direct to the horizontal and vertical electrodes of the cathode-ray tube of the oscilloscope the impulses that are obtained by recording in two directions perpendicular to one another This is done e.g in the widely used cube system introduced by Grishman [81] Another possibility is to use coefficients to change the ratio between the potentials if a system otherwise gives a component which is too great or too small, as e.g. the tetrahedron system of Wilson [238]

Many endeavours have been made to develop the vectorelectrocardiographic technique to provide the fullest possible picture of the electrical activity which occurs in the cardiac muscle, without allowing the factors caused by changes in the position of the heart or those due to the different anatomy of the surrounding tissues to affect this picture to any appreciable extent. In other words, *the aim is to have the same electrical event always to cause a Vcg loop with the same configuration* even if its position changes in accordance with the changed position of the heart. The configuration of the QRSaË loop is a very important piece of information which can be obtained only by the vectorial technique. It was shown in very fine experimental form by Burch et al. [29] that this configuration is impossible to determine even approximately from scalar leads.

Much closer to the above target are the newer so-called *corrected lead systems* in which the number of electrodes is greater and in which the potentials they emit are transformed in resistance-combining network prior to amplification. Obviously *the greater the number of electrodes, the more* accurate the results will be [149]. In planning such systems several experimental set-ups have been arranged in which the heart has been replaced by an artificial heart and the impulses it generates to electrodes on the surface of the skin have been measured [28, 230]. Instead of human cadavers, homogeneous torso models and also non-homogeneous phantom more reminiscent of man have been employed [26, 27, 28, 62, 63, 67, 68]. Fluid mappers and conducting paper mannikins have also been used [148]. The heterogeneity *of* the organism as an electric conductor interferes with all electric recordings from the skin. For instance, the quantity of lung tissue and the air content between the heart and the electrode affect considerably the amplitudes to be recorded. *Inspiratory* breath holding thus decreases the mean total QRS and T voltages in adults [17]. In addition to anatomic differences, factors such as anemia and polycythemia have also been found to influence conductivity [15]. No artificial model nor human cadaver therefore, can duplicate perfectly the conditions in living being.

The sagittal component is most susceptible to errors. A factor which distorts especially this, but *also* the *other* components, is the great difference between the so-called *image surface* and the physical human surface. The concept of image surface was introduced in 1948 by Burger and van Milaan [28]. It was reviewed and its applications discussed extensively and comprehensively by Frank [62]. With the physical human surface, the greatest distortion occurs in the sagittal component because on the image surface immediately precordially there is very large swelling anteriorly to the left, and the difference from the human physical surface is therefore greatest there. This also explains why the placing of the precordial electrodes is the most critical aspect. In other words, inaccuracy in this procedure causes greater than usual error in the recording.

Another disturbing factor which affects the sagittal component particularly is the so-called *proximity effect*. The fundamental *dipole theory is not fully valid* when electric impulses from the heart are recorded very near the heart, as with some thorax leads of the ordinary Ecg. In this respect, there is an especially great factor of error in the newborn as the heart is even closer to the electrode than it is in adults [123]. The dispersion of the Vcg recordings of newborn *infants is generally* greater than that in older subjects [80, 225]. Yet, Grant came to the conclusion that the potential differences which both Ecg and Vcg measure derive chiefly from the entire electrical field of the heart and not to any great extent from the part of the heart which is closest

to the electrode [74] He compared the location of the mean spatial vectors of loops recorded by the tetrahedron method and the transitional zones of scalar thorax leads and found that they were very close to one another [75] By measuring cancellation potentials, Frank concluded that the QRS complex as recorded from all parts of the human body can be considered to arise from a fixed location equivalent heart dipole to an average accuracy of 5 per cent. [64] This calls in question the existence of the proximity effect. The same conclusion was arrived at by Wilson et al. [241] Schaefer [196] and Schmitt et al. [211] who considered that on the whole the heart can be understood to correspond to one large dipole. On the other hand, Schmitt showed that vectorial lead systems now in common use discriminate by a factor of typically 2 1 between some regions within the heart. [210] The proximity effect thus cannot be ruled out completely

Mention should be made here of the two most important theoretical principles applied in developing corrected lead systems.

The systems of Schmitt and Frank are based on the *fixed-position dipole and image surface theory* [65 212] The aim is to reduce the number of errors caused by individual variations by manipulating them until they cancel out as far as possible. This can be done by placing several electrodes instead of a single one at critical points and leading the impulses of all of them to a network devised from a homogeneous and accurate model of a human torso of natural size. Methods of this kind have been described in many connections [62, 63, 67 212]

The lead field concept of McFee and Johnston is another principle on which corrected Vcg lead systems have been based [147 148, 149] If we measure the difference in potential which is recorded in the sagittal direction between two electrodes, one placed precordially and the other postcordially at the back, the maximum potential difference is usually elicited when the straight line connecting these electrodes passes via the hypothetical electrical centre point of the heart. The lead is called axial in this case. But if the straight line by passes the electrical centre point, the lead is non axial These authors showed that the field of the axial type will change considerably less than that of the non axial type when the relative position of the heart and electrodes is altered

When the sagittal potential difference is recorded by two electrodes it is nearly impossible to know axial degree of the lead employed since the position of the heart differs in different people. This problem can be solved partially and the proximity effect be partially eliminated by using several electrodes instead of only one and recording their average potentials. As the precordial electrode is the most critical, several electrodes are substituted especially for it, as in the system described by McFee and Parungao [150] Or as in Helm's system, it is replaced by a large electrode [91] If straight lines are drawn from all the precordial electrodes to the dorsal electrode, one of them will run close to the hypothetical electrical centre of the heart and is thus approximately axial Which of these electrodes is situated axially with the dorsal electrode does not influence the configuration of the Vcg loop since the impulses of all of them are combined in the resistance-combining network.

Wilson's tetrahedron system is the oldest of the Vcg systems still in use [238] The system is based on Einthoven's *principle of an equilateral triangle* This gives it the advantage of easy comparison with the Ecg findings of conventional limb leads. However it is generally agreed today that Einthoven's equilateral triangle principle is not adequate as such. The lead vectors are of different sizes and it should be replaced by a non-equilateral triangle Burger's triangle Strictly speaking, then, Wilson's Vcg system cannot by entirely adequate either

In this system the electrodes are fixed to the limbs like ordinary *Ecg limb leads*, and an additional electrode is applied on the back to the left of the 7th thoracic vertebra. This gives a *spatial figure* anatomically roughly the shape of a tetrahedron. The transverse component (X) is registered in correspondence with Ecg limb lead I. The vertical component (Y) is registered from between Wilson's central terminal (CT) and the left lower limb. The sagittal component is obtained from between CT and the dorsal electrode. The different components are amplified in agreement with different standardising coefficients so that when the coefficient of the transverse component is 1 that of the vertical component is 1.7 and of the sagittal component 1.2.

Another system which is based on *Einthoven's principle of the equilateral triangle* is that of *Milovanovich* [44]. The electrode sites in the frontal plane are the same as in the preceding system. But there are two additional thoracic electrodes for recording the sagittal component.

Burger's B W₁ system is also based on the triangular principle [24]. The electrode applications are again the same as in the conventional Ecg for recording in the frontal plane. For recording the sagittal component, the electrodes are applied to *the middle* of the chest anteriorly at the axillary level and dorsally at the same site as in Wilson's tetrahedron system. The two *systems* B_1 and B_2 previously introduced by Burger [29] are prototypes of this system.

Another principle in the application *of electrodes is anatomical orthogonality*. In the systems based on this principle the straight lines joining the electrodes are *orthogonal*.

Schellong used a simple lead system in which the electrodes were situated orthogonally three on the anterior surface of the trunk and one on the dorsal side [200]. In order to obtain a stereoscopic image the dorsal electrode was moved from above the left scapula to above the right scapula and the two loops obtained were viewed stereoscopically.

In the *double cube system* of *Duchosal and Sulzer* the electrodes are placed on the trunk surface at the four apices of an imaginary double cube [49]. The components are recorded parallel to the edges of the cube.

A much more commonly used orthogonal system is *Grishman's cube system* [79, 81, 208]. The electrodes are placed at the four apices of an imaginary cube: on the right posterior axillary line level with the second lumbar vertebra, *at the corresponding* site on the left, on the right anterior axillary line at the same level, and *above the right* scapula. The components are recorded parallel to the edges of this cube. In this, as in the preceding orthogonal systems, all the components are recorded with the same amplification so that no standardisation coefficients are necessary.

There are considerable inaccuracies in all the fairly simple methods described above. Newer *corrected systems* come nearer to the ideal that a *similar* electrical phenomenon in the

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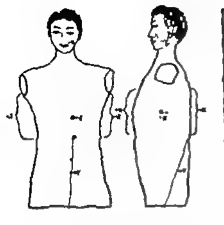


Fig. 2. Application of the electrodes in Helm system. The dotted area is covered by large sponge electrode and on the other side of the trunk there is an ordinary small electrode, placed at the corresponding site. The vertical component is recorded between the electrode on the forehead and the electrodes on the left lower limb and at the terminal point of the line marked Y on the back.

obtained as when the same skin area was covered by a single large electrode.

The positioning of the electrodes in *this system is illustrated in Fig. 2.* Sponge electrodes dipped in physiological saline solution are applied to marked sites so that they are just not interconnected. Opposite each sponge electrode is a normal metal electrode on the other side of the trunk.

Dower and Osborne were particularly anxious to evolve a method which would be as practical as possible and at the same time sufficiently accurate [45]. Their system has four electrodes, theoretically the smallest number for Vcg recording. In this system, too, the impulses are led to a resistance-combining network devised from a torso model. This set-up, according to the authors, gives very good results when the results obtained with Frank's system are used as the basis of evaluation. It is, of course *impossible to achieve exactly the same* standard of accuracy. The authors recommend the use of this system for patients in poor condition to avoid the strain of examination.

The system of McFee and Parungao [150] is based on the theory of lead field advanced by McFee and Johnston [147, 148, 149] and on the view that a roughly axial lead is easier to achieve if a series of electrodes is used rather than a single electrode (see page 12). The theoretical basis is actually not appreciably different from the principle of Helm's system.

The electrode locations are shown in Fig. 3. The transverse component is recorded between an electrode on the right flank and a pair of electrodes on the left flank. Viewed from the side they are located 1/3 of the thorax width from the anterior wall of the *thorax and are directly opposite one* another. The distance between the electrodes on the left flank in an adult of medium size is 11 cm. The sagittal component is recorded between the three precordial electrodes and the electrode at the corresponding site on the dorsal side. The precordial electrodes form an equilateral triangle. In a medium sized adult they are 6 cm from the centre of a triangle drawn directly above the centre of gravity of the ventricles. The site of course varies with the individual, *but a point* 2 cm to the left of the left margin of the sternum in the 5th *intercostal* space is selected for routine use. The

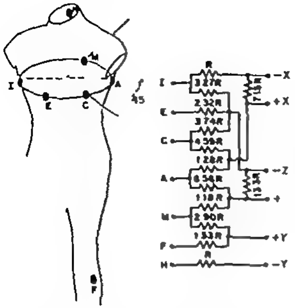


Fig. 1. Application of the electrodes and the resistance-combining network in Frank's system.

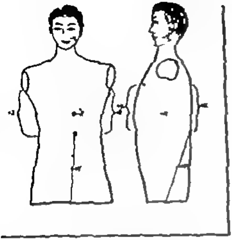
heart will always generate a Vcg loop of the same shape whatever the position of the heart and other anatomical differences.

Schmitt's SVEC III system incorporates 14 electrodes and a resistance-combining network [212]. This method gives very accurate tracings, but the great number of electrodes makes it impracticable for clinical use. It is often used for the comparison of different systems to evaluate other simpler methods.

Frank's system requires the use of seven electrodes [65]. Five are in the same horizontal plane at the level of the heart around the thorax: immediately to the front, immediately back or left of the spine, on both mid-axillary lines and 45 degrees anteriorly and to the left on the same level, and on the neck or forehead and the left lower limb. The conductors are connected with the electrical network as shown in Fig. 1. The transversal component is formed by the three thoracic electrodes, the vertical component by the electrodes of the head, back and the left lower limb and the sagittal component by all five electrodes on the chest. The placement of the electrodes is fairly simple in Frank's system and the results are quite accurate. The system is consequently widely used.

Frank and Seiden sought to evolve a simple method from Frank's system [69]. They used the same electrode location as in Wilson's tetrahedron system and a resistance-combining network designed from model measurements. They compared the results with those obtained by Frank's 7-electrode system. The results were fairly similar in some of the cases but rather divergent in others, and thus the system has not gained greater use. A detailed analysis of this system has been reported by Frank [66].

Helm's system [91] is based on the principle that more consistent lead vectors are obtained when recording between two networks of points than when recording between two individual points (see page 12). Helm had already stated this earlier [89, 90]. In other words, it is possible in this way to have fairly similar vector properties for the different parts of the heart. He also noted that when the number of electrodes placed at even distances in a certain area was increased their average potential grew at an increasingly slower rate until the curve illustrating the potentials approached the horizontal. The same potential was



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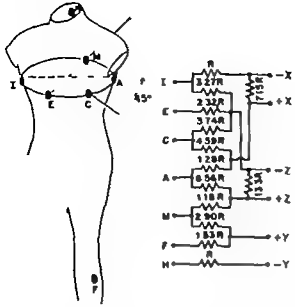

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COMPARISON OF DIFFERENT SYSTEMS

One difficulty in practical Vcg work is the multiplicity of the recording systems. No system is perfect. It is necessary especially when studying the newborn, to take into consideration the demands of practicality simplicity and speed in addition to theoretical faultlessness. When scalar Ecg is compared with Vcg a point often mentioned in its favour is that the placing of the electrodes is simple and clinically a well-known procedure. But it must also be remembered that no endeavour is then made to reduce the considerable factors of error which should be kept in mind in the interpretation of every Ecg curve. If the same criteria were considered adequate for the Vcg, an equally simple recording system could be used. But in order to reduce the factors of error efforts have been made to evolve new more nearly perfect systems. It is of course possible also to perform scalar recordings by corrected systems and obtain more accurate results than the routine Ecg technique gives. The multiplicity of systems is thus not a problem specific to vectorcardiography. It applies to the recording of electrical cardiac funtion in general, whether the recording technique is scalar or vectorial.

Burger et al. compared their own two systems (B_1 and B_2) with Wilson tetrahedron system [29]. As the coefficients of their systems were determined by model measurements and lead to fairly consistent results, while the results of the tetrahedron system differed more from them, these authors regarded their own methods as superior to the tetrahedron system.

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Recordings were performed by Abildskov and Pence using the tetrahedron system and the corrected system of McFee and Johnston [1]. The results obtained by the latter were much more consistent. The normal recordings were usually fairly similar but if there was an unusually great axis deviation to the right the tetrahedron recording showed very marked dispersion.

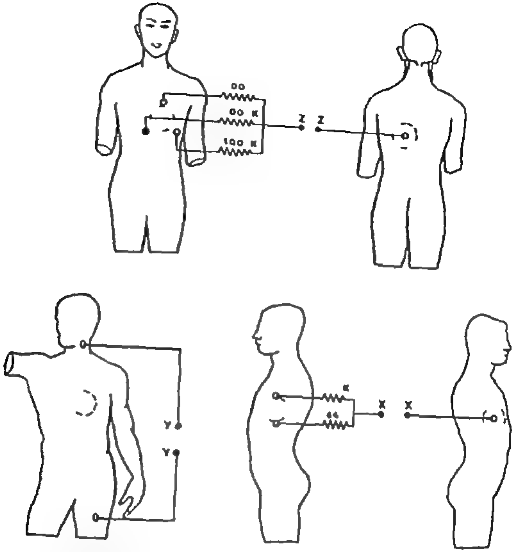

Fig. 3. Application of the electrodes and the resistance-combining network in the system of McFee and Parungao.

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In the system introduced by *Halmos et al.* the electrode locations are not fixed anatomically but are applied according to the position of the heart [86] This system is anatomically orthogonal.

Of the *other recording systems* mention may be made of Kimura's orthogonal system which is still in use in Japan [116] Milnor's orthogonal system [152 154] Akulynchev's system, almost the only one used in Russia [3] in which, differently from all the other systems, recording is at five planes and the electrodes are located in roughly the form of a pyramid, and Barber's system [14] which is based on the lead field concept of

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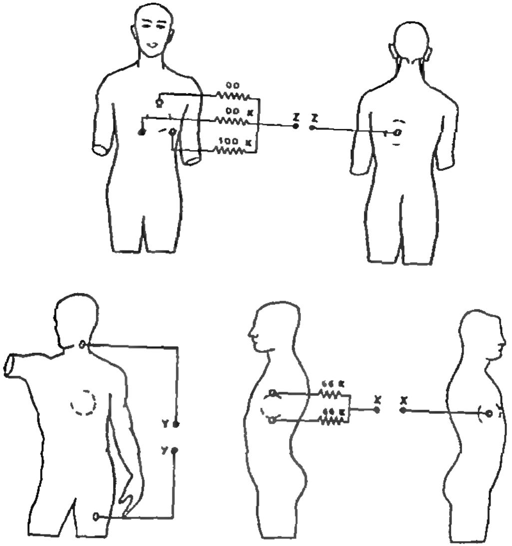

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Burger *et al.* compared two systems based on the tetrahedron technique but in which the sagittal component was determined between CT and a dorsal electrode or a thoracic electrode [30] Provided suitable coefficients were selected, the results of both systems were fairly similar The authors recommended for general use also coefficients that can be determined by calculation or experimentally They claimed in another context, that any well founded Vcg system can be converted with the help of coefficients to make it comparable with another system without changing the location of the electrodes [25] Such a conversion cannot be achieved by changing the placement of the electrodes [24]

Dower and Osborne compared the system introduced by Frank and Seiden and their own system, using Frank s 7-electrode system as the criterion [45] Four electrodes are used in both systems, the aim being simplicity They found that their own system was superior and recommended it for patients in poor condition.

Four very accurate systems, viz. those of Schmitt, Frank, McFee and Parungao and Helm, were compared by *Langner et al.* [128] All four gave fairly consistent results *for the majority of the test objects*, but whenever there was a greater degree *of* divergence it occurred in the sagittal component and was generally seen in abnormal recordings. When this occurred, the Schmitt and Frank recordings were similar to one another and those performed according to Helm and McFee were like one another This could be expected from the theoretical bases of the systems.

Pipberger performed orthogonal Ecg and Vcg recordings on 100 normal persons using Schmitt s SVEC III system. He compared the results with Ecg curves obtained with conventional leads. The dispersion in the frontal plane was about 50 per cent smaller in the SVEC III curves when assessed on the basis *of the maximal QRS vector* [174]

Burger et l. compared results that they obtained using Frank s, Schmitt s and their own system (B_1W_4) [31] The correlation between the Frank and Schmitt systems was fairly good, while their own system gave results which differed *materially from them.* It must be remembered, *however that fewer* electrodes are used in their own system than in the other two. They emphasised that the sagittal component of the heart vector is the most difficult to record.

Comparing the systems of Kimura and of Grishman (cube) Kimura and Toshima noted that the former was more sensitive to hypertrophy of the left and the latter to hypertrophy of the right heart [117]

The practical value of Frank s and McFee s and of the cube and tetrahedron systems *for* infants and children was studied by Hayashi and Takarada. *They* stated that the Frank lead system of vectorcardiography seemed to be applicable, roughly without distortions, to the majority of infants and children, regardless of healthy or sick ones [87]

Helm and Te-Chuan Chou experimented with changing the dipole location of corrected and uncorrected vectorcardiographic leads, using Frank s system as the corrected and a *slightly modified* cube system as the uncorrected system [93] Although the loop configuration failed in both systems to remain unaltered when the dipole location was changed, Frank s method proved superior The experiments were conducted on a torso model.

It is difficult to find adequate standards for evaluating the reliability of the different systems. For instance a basis commonly used is the degree of *similarity* as compared with the results obtained by methods generally recognised as good. In some cases the comparison *has* been with *loops* or mean vectors constructed from an ordinary Ecg [87 214 216] Another standard *that has been used is the* consistency of the results obtained by a method for a consistent test group. Pair determinations on the same sub-

ject form a still more *critical* basis. In the author's opinion, the latter two are *the only* unbiased criteria since systems based on the same theoretical foundation usually give fairly similar results irrespective of how accurate they are. Furthermore, it can probably be assumed from the studies cited here that when one's own method is compared with another the former is usually found superior.

ELECTROCARDIOGRAPHIC STUDIES ON THE NEWBORN

Electrocardiographic studies on full-term newborn

The electrical activity of the heart of the newborn has been studied extensively with the aid of scalar Ecg. Certain special features have been discerned compared with recordings made later in life. Consequently it is not correct to draw a line between the normal and the pathologic according to the same rules.

Normal Ecg values of the newborn have been reported by e.g. Hori et al. [101], Groedel and Miller [82], Ashman and Hull [10], Joly and Combe [110], Schaffer et al. [199], Ziegler [248], Datey and Bharucha [39], Kessel [114], Heck and Stoermer [88], Michaelsson [151], Rothfeld et al. [189], Nadas [157], Wasserburger [232] and Walsh [227]. The Ecg of the newborn differs from the Ecg later in life in many ways. The most important of these differences are:

Preponderance of the right heart which in older subjects would be taken as a sign of pathologically marked right axis deviation or right ventricular hypertrophy. It is a physiologic phenomenon in the newborn, associated with the anatomic size of the ventricles and their work output. According to Ziegler, both ventricles of the heart are of roughly equal weight in a fetus of 24—28 weeks and their work output, obviously, is also the same [250]. Emery and MacDonald stated that there is left ventricular preponderance in the fetus until the age of 24 weeks [57]. After 24—28 weeks of fetal age, the mass of the right ventricle grows relatively more rapidly in weight and at the time of birth is heavier, though only slightly heavier, than the left ventricle. However, the wall of the left ventricle is thicker than that of the right already at this time. After birth, the left ventricle grows more rapidly than the right and the adult weight ratio between the right and left heart is reached at the age of c. 6 months [250]. Keen found that the left heart was heavier than the right heart at the age of 4 weeks in a newborn delivered at term [113]; this has been confirmed by Emery and Mithal [58].

Abnormally high peaked P waves have been demonstrated in newborn normally during the first three days of life [38]. P waves over 2.5 mV in height and longer than 0.07 sec. in duration have been regarded as pathologic in the newborn [157, 199]. The duration of the P wave increases with age as the auricular mass increases.

A prominent Q wave in healthy newborn in leads II and III has been noted by several workers [101 110 114 119 219] A Q wave in lead V_1 is considered to signify hypertrophy of the right heart in the newborn as well [146 157] Walsh stated that the presence of a Q wave in V_1R is normal though rare [228]

The T wave is of special interest in the newborn. It is normally positive in lead V_1 during the first day of life and then negative for several years. This was attributed by Ziegler to elevation of pressure in the right heart [249] Stern and Lind noted that the inversion of the T wave occurs over a wide range of neonatal age from about 30 min. to 96 hours in a material of 32 children [218] Later in the neonatal period the positive T wave is always pathologic in lead V_1 [120] The newborn often shows very low T waves in the limb leads [151] The very early neonatal Ecg changes were studied by Hait and Gasul. They found that the T wave was negative at the age of under 5 min. in lead V_1 and positive after it, maximally at the age of 6 hours [84] They attributed this to transient ischemia or at least overloading of the right heart.

The PR interval is much shorter in the newborn than later in life. But prolonged PR intervals have been reported during the first week, and especially during the first hour of life [41 191 228] It has been assumed that this is due to the immaturity of the conduction system [191]

The QT interval may be prolonged in some healthy newborn during the first days of life [151]

The QRS interval is naturally shorter in the newborn than in older subjects since it depends on the volume of the cardiac muscle mass. It, too, is sometimes longer than normal in the first week of life [41] as is the *ST segment* [228]

Arrhythmias are more frequent in the newborn than in later life. Michaelsson's study showed a very high incidence of sinus arrhythmias and supraventricular arrhythmias in newborn infants [151] In contrast, extrasystoles occur more rarely in newborn than in older subjects [124, 156]

No difference was observed by Ringel between the electrocardiograms of a normal and an asphyxiated newborn [186] but Stern and Lind reported a more marked deviation to the right of the electrical axis of the heart in asphyxiated newborn infants [219] In studies on the isolated right auricle of the rabbit Hirvonen stated a prolonged QRS interval, lowered R deflection and a retarded beat rate in anoxia [95] No significant differences have been noted before and after the newborn infant's first cry [251] Electrocardiograms taken during the fetal period and again after birth have revealed no major or sudden changes in connection with birth [109 220 231] Nor have any such changes in heart rhythm been noted [73] Birth obviously places no exceptionally great strain on the infant's heart. Adams and Lind showed by catheterisation that postnatal pressure variations in the heart occur only gradually in the course of a few days [2] and not instantaneously as had

been earlier assumed. The decrease in pulmonary arterial pressure after respiration has begun spontaneously was studied by Peltonen and Hirvonen in lambs born by cesarean section [168]. No sudden changes occurred. The volume of blood in the lungs of young lambs increases by only c. 20—30 per cent after the first breath of life, and not for 24—36 hours is a 100 per cent increase observed [4]. The situation is the same with both aortic and pulmonary arterial pressure, no rapid pressure changes occur perinatally [96, 168]. Nor are the fetal circulatory shunts closed instantaneously after birth [97, 98, 164, 165, 166, 167, 168, 169, 170]. It is understandable, then, that the Ecg displays no acute changes in connection with birth. An exception, however, is the alterations in the T wave in infants during the first minutes of life [84]. But the Ecg changes during the neonatal period are much more rapid than they are later and the dispersion of normal values is greater. Hence, it is often more difficult to distinguish between normal and pathologic at this time than later in life. Recording of serial tracings is therefore recommended in doubtful cases [230].

Electrocardiographic studies on prematures

Whether the Ecg of the newborn premature has certain typical features to distinguish it from that of a full-term baby is a matter that has engaged the attention of many authors for some time. In 1913, Noeggerath came to the conclusion that good cardiac function is generally associated with a normal electrocardiogram, whereas premature or otherwise weak babies may give abnormal curves [160]. Räihä came to a similar conclusion in his study on electrocardiography of premature infants [190]. He also noted that so-called primitive curves with low P and T waves and, occasionally abnormally low amplitudes in all waves, were often encountered in prematures. The same observation was made by e.g. Burghard and Wunnerlich [33].

The electrical axis of the heart shows a smaller deviation to the right during the first weeks of life in the premature than in the full-term newborn [190, 192, 224]. The very low waves of the QRS complex registered in some prematures during the first week of life do not persist, but change to normal at the age of 1—2 weeks [227]. In the thorax leads on the left, prematures display a higher R wave and deeper Q wave on the average than are seen in newborn delivered at term [193].

The PR interval is slightly shorter in newborn prematures, 0.092—0.1 seconds [221, 224], than in full-term infants of the same age, 0.08—0.12 seconds [18, 82, 83, 114], although prolonged intervals are recorded for both, especially during the first week of life [41, 191, 192, 224].

The QRS interval is also a little shorter in the premature newborn. 0.050 seconds may be regarded as the

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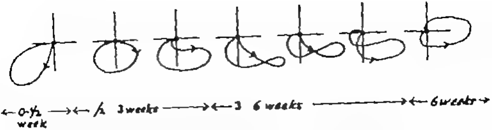

Fig. 4. A series of horizontal QRS loops recorded by Elek *et al.* by the double cube method [53]. The loops display typical changes of infancy and early childhood.

distinct signs of hypertrophy of the right heart. Progressive changes in the Vcg began to appear from age of a few days, and at 1 month the differences from the recordings of the first days of the infant's life were fairly distinct. Individual differences were great. Slower progression occurred from the age of 3 months on. The authors realised the inadequacy and inaccuracy of the methods employed for study of the newborn, particularly as regards the horizontal projection, which varied over an extremely great range in the tetrahedron system, and the greatly exaggerated right heart effect obtained in the cube system. In contrast, the frontal loop recorded by the cube system was more to the left and much smaller than that recorded by the tetrahedron system. Very great dispersion was obtained by both methods. There was no progression in the T wave during the neonatal period. Labrunie tried to construct the Vcg loops from the scalar Ecgs of a fairly small group of newborn and arrived at results which resembled the above in their main outlines. The dispersion was very great and the results rather summary [121].

Rothfeld *et al.* [189] and Wachtel *et al.* [225] studied 50 healthy infants immediately after delivery and 31 of them at the age of 1 month, using the cube system. The finding for normal newborn under 48 hours old was reminiscent of hypertrophy of the right heart, as in other studies, but with the difference that in these studies the QRS and T loops were almost always concordant at all planes and that the direction of inscription of the QRS loop was generally clockwise at the sagittal plane. As variations, these authors mentioned the cases in which the QRSaE loop was left, superior or posterior or in which the direction of inscription of its frontal or horizontal projections was counter-clockwise.

Using the cube system, Calleja *et al.* made 166 Vcg tracings of 154 children, some of whom were newborn [34]. They found that the development of the finding with age was seen best in the horizontal projection, although no manifest development could be stated during the neonatal period. The average angle formed by the mean QRS vector and the ground line immediately after delivery and at the age

upper limit [222, 224] while for full-term babies it is 0.065 seconds [88].

Besides the low *P waves* already mentioned, prematures often have high and peaked P waves [227, 234] and sometimes negative P waves in leads V_1 and V_2 [193].

Although the *T wave* in lead V_1 is generally positive in newborn delivered at term during the first day of life except for the first few minutes [84], it is often negative in the first day of life of prematures [193]. Prematures have biphasic and negative T waves in all bipolar leads more often than newborn delivered at term [182, 193].

Arrhythmias in newborn prematures have been studied recently by means of continuous recording on magnetophone tape. Morgan *et al.* studied 20 normal prematures aged from 5 hours to 29 days [155]. Many sinus arrhythmias were elicited from 5-hour recordings. Nearly half of the prematures had a rhythm that was 50 per cent slower than normal, and five infants had in addition one or more periods of especially slow bradycardia, i.e. under 50/min. Bradycardia generally occurs during sleep, sometimes in connection with defecation. Välimäki noted transient sinus bradycardia in almost every premature when the continuous recording was performed sufficiently long [246].

Thus, although there are certain electrocardiographic differences between the premature and full-term newborn, they are not the rule and they are not typical enough to warrant the listing of definite Ecg characteristics of premature infants.

EARLIER STUDIES OF THE VECTORCARDIOGRAM OF THE NEWBORN

Several workers have studied the Vcg of infants, but the materials have usually been small and most of the recording systems used have been the old ones which are too inaccurate for reliable results, especially with newborn infants. No uniform idea has been formulated concerning the vectorcardiographic technique and the results for normal newborn.

Schaffer and Beinfield studied 35 newborn by Grishman's cube system and established a pattern similar to that seen in older persons with hypertrophy of the right heart [197]. Forty-seven infants were studied by Elek *et al.* using the double cube system of Duchosal and Sulzer. They reported the same phenomenon and drew attention to the accentuation of the potentials of the left heart from the age of 20—30 days onwards [52]. The age of the subjects in this material was from 2 days to 2 years. The authors described the development of the Vcg finding in healthy full-term infants as is depicted in Fig. 4.

The cube system was used by Doll, too, in his study of 61 newborn. He also established the same type as in hypertrophy of the right heart later [42].

Rosen and Gardberg introduced the largest material so far, 300 infants, aged 1 day to 1 month [188]. The vectorcardiograms were made by Grishman's cube and Wilson's tetrahedron systems. Again, there were

term infants; c) more right ventricular dominance at the age of 72 hours and one week than in full term infants; and d) greater variability in all age groups but especially during the first week of life. [139]

Fowler made Vcgs of 50 normal infants *from birth to 1 year of age*. He used an Electronics for Medicine DR-8 recorder which gives results reproducible with the Frank lead system. The dispersion was greatest in the youngest infants. The spatial QRS-T angle (see p. 28) at an age of under 2 months was 71 degrees, standard deviation 29 degrees. There were no distinct differences between the different age groups in the magnitude of the instantaneous and maximal vectors. [60]

ANALYSIS OF VECTORCARDIOGRAPHIC FINDINGS

QRSsE *half area vector*

Maximal vector, half time vector and half area vector etc. have been used in the attempt to find vectors that characterise Vcg loops. The aim has been to find a vector that is as consistent as possible with the so-called mean vector which is the integration of the magnitude and time of all spatial instantaneous vectors during QRS. The approximate mean vector can be determined from scalar Ecg by indicating the superficial areas of the waves by vectors and from Vcg by taking the mean of a number of instantaneous vectors determined at even and very short intervals [173]. Pipberger determined in this way the mean spatial QRS vectors for 34 *persons* and obtained values which were close to the mean vectors obtained from scalar Ecg [173]. *He noted* in the same study that maximal vectors and half time vectors were inconsistent and inaccurate when compared with mean vectors. On the other hand, half area vectors showed extremely good correlation with mean vectors as regards vector direction. Accuracy was increased by averaging the 3 planar vectors. This can be done by calculating the mean time for *half* area vectors on each plane. Other authors, too, have reported that the half area vector is more stable than the maximal vector especially in sagittal and horizontal projections [105].

QRSsE polar vector

The QRSsE loop is usually on roughly the same plane, the so-called QRS plane (152, 175, 187, 201). The position of this plane naturally varies in individuals, which increases the variations of the QRS loop on the ordinary recording planes. But if the QRS loop is examined on its own plane the range of variation is much smaller [152, 175, 185]. It is fairly easy in *practice to determine* the plane in question and the projection of the QRSsE loop on it by *using a vector loop rotator or resolver* [209]. Burger and Vaane *introduced the concept* of polar vector. It means a vector perpendicular to the QRS plane; its base is at the zero point of the QRSsE loop and its length is directly proportional to the area of the QRS

of 1 month was +90 and +60 degrees in the frontal projection +53 and +57 degrees in the sagittal projection, and +85 and +40 degrees in horizontal projection. The progressive turning of the mean QRS vector to the left and posteriorly continued after this in the tracings taken at the age of 3 months. The dispersion of the results was greatest in the youngest group

Vcgs of 90 normal newborn were taken by Namin *et al.* by Frank's system [159] The angle formed by the mean frontal QRS vector and the ground line was 138 ± 33.6 degrees during the first day of life subsequently turning progressively to the left. The initial 0.005 instantaneous vector was determined in the horizontal projection and its direction immediately after birth was 89 ± 23 degrees; it then turned progressively to the right. The direction of inscription of the QRS loop in the horizontal projection was counter-clockwise in 10 infants, clockwise in the others. The mean T axis was chiefly anterior on the first day of life subsequently turning to the left. DePasquale and Burch made Vcg recordings of 50 newborn by the tetrahedron system [41] They observed that the TsE loop deviated progressively from right to left during the first 86 hours of the infant's life

Schmitt's Vcg system has also been used for vectorcardiographic study of the newborn. It was employed by Elliott *et al.* on 50 infants. One of their findings was that the direction of inscription of the horizontal projection in the newborn was almost always clockwise as established by other systems, too [55]

Using Frank's system, Namin *et al.* took Vcgs of 107 normal infants aged from a few hours to 18 months [158] They made serial tracings for some of the infants. The under 1 month age group revealed a very great dispersion. These authors contend that serial tracings must always be done for the newborn in ambiguous cases.

A very interesting experiment was performed by Idriss et al. on mongrel bitches. Applying Frank's system, and using a special surgical technique they made Vcg tracings before birth and followed the changes occurring after birth. The maximal QRS vector was directed upwards to the right and anteriorly before birth. The changes occurred gradually and not instantaneously during the transition to extrauterine environment, and it was not until the 2nd day of life that the maximal QRS vector was directed increasingly down to the left as in the second week of life Only minimal alterations occurred in the pressure of the right heart during the transition to extrauterine environment. [109] The same phenomenon in regard to pressure has been established in human beings (see p. 20)

Liebman *et al.* used Frank's system to make Vcgs of 50 normal prematures at the age of 24 hours, 72 hours, one week and one month. They continued the study beyond the neonatal period. Their most important results were as follows. a) smaller voltages than for infants born at term b) less right ventricular dominance at the age of 24 hours than in full

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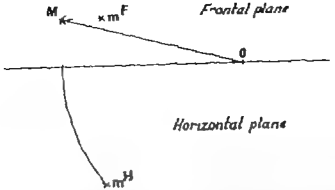

Fig. 5. Revolution to determine the spherical coordinates and spatial magnitude of vector according to Brinberg (19). m^F and m^H are the projections of the terminus of the vector in the frontal and horizontal planes. The azimuth is measured directly from the horizontal projection. The spatial vector is then assumed to be turned into the frontal plane so that its magnitude and the angle formed by it with the horizontal plane remain unchanged. Thus gives vector OM. Its magnitude is the same as the spatial magnitude of the original vector. Elevation is the angle between vector OM and the ground line.

changes of the heart, but is determined solely by the properties of the myocardium [76].

The spatial QRS-T angle can be determined by many methods. It can be calculated from the projections of the mean QRS and T vectors on the planes as follows:

If
V_1 = the spatial magnitude of the mean QRS vector
X_1, Y_1 and Z_1 = the scalar magnitudes of the above,
V_2 = the spatial magnitude of the mean T vector and
X_2, Y_2 and Z_2 = the scalar magnitudes of the above
we obtain

$$V_1 = \sqrt{X_1^2 + Y_1^2 + Z_1^2} \text{ and}$$

$$V_2 = \sqrt{X_2^2 + Y_2^2 + Z_2^2}$$

If we use the expression of the scalar product of the vectors, we obtain the spatial QRS-T angle (φ) as follows:

$$\cos \varphi = \frac{X_1X_2 + Y_1Y_2 + Z_1Z_2}{V_1V_2}$$

Langner constructed a geometrical model which can be used to determine the directions of the mean spatial vectors and the angles between them [125]. The spatial QRS-T angle is obtained very simply from the tables compiled by Helm and Fowler in which the QRS-T angles on different planes are entered [92]. The spatial angle is then obtained through a simple process of calculation. According to Brinberg, the spatial QRS-T angle is determined in the following way: The mean QRS and T vectors and the line which connects their termini form a triangle in space. The projections of the termini of both vectors on the frontal and horizontal planes are known. Their true lengths, as well as the true length of the segment of the line connecting their termini, are determined by revolution (Fig. 5) from the projections men-

loop in the projection on its own plane Seen from the direction of this vector the direction of inscription of the loop is counter-clockwise They found that the direction of the polar vector was often so different from normal in persons with heart disease that it was of diagnostic significance. [32] Polar vector was regarded by Pipberger and Carter as the best indicator between a normal and pathologic record. If the shape and principal axis of QRS and the QRS-T angle on the QRS plane were considered in addition, it was possible to establish pathologic records with 85—100 per cent reliability when using the corrected systems of Frank and Schmitt. [175]

Spatial QRS-T angle

A very important point in studying the ventricular complex of electrocardiogram is the relationship between the waves caused by depolarisation and repolarisation and the entity they constitute As early as 1934 Wilson et al. noted the areas of the waves of the ventricular complex [240] By measuring separately the surface areas on the positive and negative side planimetrically and deducting the smaller from the greater they obtained a quantity which they termed the ventricular gradient. The gradient is then naturally a planar gradient on the plane in question. By using tracings on different planes it is possible to determine also the spatial gradient. As the ventricular gradient has both a direction and a magnitude, it can be illustrated with a vector This has since become one of the most important quantitative values in Ecg analysis.

Determination of the ventricular gradient from the scalar Ecg and the factors affecting it were studied by Ashman and his co-workers [6 7 8 9] Simonson *et al.* stress the significance of spatial ventricular gradient [215] The ventricular gradient of infants was determined by DePasquale and Burch [40] though the material was small. Preponderance of the right heart was naturally revealed and the ventricular gradient was longer during the first three years than later

When analysing a vectorcardiogram it is no simple matter to determine the *ventricular gradient* chiefly because of the difficulty of determining the *duration of the T loop* As the ventricular gradient is a concept integrated with time very careful determination of time is necessary However the mutual relationship between the QRSsÊ and TsÊ loops is of equal significance in Vcg diagnosis as in scalar Ecg. This ratio is illustrated by the *spatial QRS T angle* which refers to the spatial angle constituted by the mean QRSsÊ vector and the mean TsÊ vector Its use as a fundamental criterion in Vcg interpretation was suggested by Pipberger *et al* [177 178] and Grant *et al.* [77]

The QRS-T angle is affected to some extent by the same factors as the ventricular gradient. The QRS-T angle increases very typically in many pathologic conditions, such as hypertrophies, bundle branch blocks, electrolyte disturbances and *infarctions*. It is not influenced by the positional

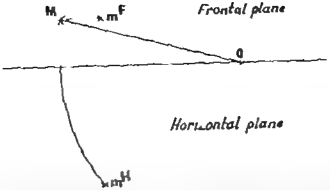

Fig. 5. Revolution to determine the spherical coordinates and spatial magnitude of vector according to Brinberg (18) m^F and m^H are the projections of the terminus of the vector m the frontal and horizontal planes. The azimuth is measured directly from the horizontal projection. The spatial vector is then assumed to be turned into the frontal plane so that its magnitude and the angle formed by it with the horizontal plane remain unchanged. This gives vector OM. Its magnitude is the same as the spatial magnitude of the original vector. Elevation is the angle between vector OM and the ground line.

changes of the heart, but is determined solely by the properties of the myocardium [76]

The spatial QRS-T angle can be determined by many methods. It can be calculated from the projections of the mean QRS and T vectors on the planes as follows:

If

V_1 = the spatial magnitude of the mean QRS vector

X_1, Y_1 and Z_1 = the scalar magnitudes of the above,

V_2 = the spatial magnitude of the mean T vector and

X_2, Y_2 and Z_2 = the scalar magnitudes of the above

we obtain

$$V_1 = \sqrt{X_1^2 + Y_1^2 + Z_1^2} \text{ and}$$

$$V_2 = \sqrt{X_2^2 + Y_2^2 + Z_2^2}$$

If we use the expression of the scalar product of the vectors, we obtain the spatial QRS-T angle (φ) as follows:

$$\cos\varphi = \frac{X_1X_2 + Y_1Y_2 + Z_1Z_2}{V_1V_2}$$

Langner constructed a geometrical model which can be used to determine the directions of the mean spatial vectors and the angles between them [125]. The spatial QRS-T angle is obtained very simply from the tables compiled by Helm and Fowler in which the QRS-T angles on different planes are entered [97]. The spatial angle is then obtained through a simple process of calculation. According to Brinberg, the spatial QRS-T angle is determined in the following way. The mean QRS and T vectors and the line which connects their termini form a triangle in space. The projections of the termini of both vectors on the frontal and horizontal planes are known. Their true lengths, as well as the true length of the segment of the line connecting their termini, are determined by revolution (Fig. 5) from the projections men-

tioned. When all the sides of the triangle are now known, the angles are obtained by calculation. [19] Another possibility is to determine the spherical coordinates of the axes of the mean QRS and T vectors by rev olution and to mark them on the spherical surface so that the spatial angle between them can be measured by a movable meridian.

The spatial QRS-T angle of 50 nor mal adults determined by Ball and Pipberger was 56 ± 18.8 the maxi mum and minimum were 20 and 105 degrees [13] Rothfeld *et al.* determined the QRS-T angle of 50 newborn in plane projections and reported it to be under 40 degrees on the frontal and sagittal planes in the majority of the cases (c. 80 per cent) and on the horizontal plane in a little over half the cases [189] Babej and Lívancová—Brožová [12] and Hiraya ma [94] stated that the QRS-T angle is largest in the neonatal period.

Other aspects of analysis

In addition to the measurable quan tities mentioned in the preceding paragraphs, several other quantities that illustrate better or less well cer tain properties of Vcg loops have also been employed for statistical and com parative work.

Several workers have determined the superficial area of the QRS loop. A simplified method has been used for this purpose by Marini [144] The body of the loop is taken to be roughly rectangular L × V in area, when L = length and W = width. The intrinsic and terminal parts are assumed to be approximately triangular and thus the area of both can be obtained from their length and width L × W 2 However as the configuration of the loops may be extremely vague this method must be regarded as too inaccurate The area is best determined planimetrically or in the absence of a planimetre e.g. by calculating on graph paper the small squares that remain inside the loop. In addition to the area of the loop, it is of course possible to determine the areas of its parts, such as the area distribution in the various spatial directions or the area swept by the vector as a function of time [5]

The ratio between the anterior and posterior part of the area of the QRS loop gives a general idea of the loca- tion of the loop in the anteroposterior direction [144] It is naturally possible in the other directions to divide the loop into two parts on either side of a certain plane i.e to determine the relationships left right or superior/in ferior The locations of the extreme anterior and posterior points and the ratio of their distances from the ground line have been determined in a cor responding way By connecting mean extreme points Paul *et al.* reconstruc ted vectorial loops which may be con- sidered to represent some kind of mean loops for the groups in ques- tion [163] Configuration types are often described simply as narrow oval, round and figure-of-eight loops. It is also important, of course to state the direction of inscription. This is most important in the horizontal projection

since it is decisive in the diagnosis of hypertrophy of the right heart (see p. 30)

A very commonly applied method is to describe separately typical parts of the loop. They are the initial portion, body and terminal appendage. They are easy to distinguish in nearly every QRS loop. The initial portion and the terminal appendage are also indicated by the *initial* and *terminal inflection points*. The loop may be divided into more parts for analysis, e.g. into four components: initial, early, late and terminal, the boundary between the two midmost portions being 0.04 seconds [70]

The inscription speed of the different portions of the QRSaÊ loop is readily observable as the time orientation is distinct, the line being broken 400 times per second. This is of primary importance in bundle branch blocks. Terminal delay in such a case is diagnostic.

A general idea of the orientation of the loop can also be obtained from the common practice of announcing the octant or quadrant within which the greatest part of it is located [130, 131] or also the sextant [53] if only a projection on a certain plane is meant.

A very practical mode of representing spatial vectors and loops for analysis is to present them on a spherical surface [19]. The points at which the vector axes intersect the spherical surface are marked with spots of varying size, the radius of which is directly proportional to the magnitude of the vector in question. The loop can thus be depicted by marking a number of instantaneous vectors. As the QRSaÊ loop is on roughly the same plane, an arrow may be drawn on the spherical surface to show the orientation, slope and rotation of this plane. According to Brinberg [19] a loop can thus be denoted e.g. as follows: 45 7 *NE 30*. This means *that the mean vector axis of* the loop in question is on the spherical surface at 45 degrees longitude and 7 degrees latitude and that the body of the loop is travelling north-easterly and forms an angle of 30 degrees with the meridian of its position, which in this case is the 45 degree meridian [19]. Although terms such as longitude, latitude and the points of the compass are not very commonly used in vectorcardiography, they are very clear and useful when the sphere is used as the frame of reference.

Although the QRSaÊ loop is in fact on roughly one and the same plane some of its parts deviate from this plane to a greater or lesser extent. The magnitude of these deviations is illustrated by the tortuosity. It is determined by placing a movable meridian on the plane of QRS on the spherical surface and measuring the maximum deviation of the QRSaÊ loop from this plane to both sides. Tortuosity is then the sum of both these deviations in terms of degrees. The tortuosity of the loop portions can be determined in the same way [19]

Electronic computers have often been employed recently to analyse electrocardiographic and vectorcardiographic findings. The subject has been discussed by Pipberger *et al.* [176, 179] among others.

DIAGNOSTIC POSSIBILITIES OF VECTORCARDIOGRAPHY

The diagnostic possibilities of vectorcardiography are regarded as distinctly superior to those of scalar electrocardiography in some areas. This is apparent from even a brief review of the literature.

Hypertrophy of the right heart (RVH) can sometimes be manifested very untypically in Ecg, and Vcg is necessary to establish the diagnosis [128, 129 130]. According to Elek *et al.* who reported on 34 cases, Vcg is correlated better than scalar Ecg with the work of the right heart [53]. Richman and Wolff demonstrated easily interpretable changes in the Vcg of patients with congenital heart disease who had RVH [184]. In the material of Massie and Walsh, which includes 25 patients with isolated pulmonary stenosis, scalar Ecg displayed signs of right ventricular hypertrophy in about two-thirds of the cases whereas Vcg revealed them in all the cases [146]. In the same authors material of 239 patients with secundum type ASD scalar Ecg revealed hypertrophy of the right heart in c. 30 per cent and Vcg in 95 per cent of the cases [146]. A reliable vectorcardiographic diagnosis of RVH is very important also for evaluation of operative results and, furthermore, reduces the need for repeated catheterisation [80]. Vcg has also been held to be a suitable method for assessing the severity of pulmonary stenosis [207 247] and as an indicator of RVH in patients who have pulmonary stenosis with or without a ventricular septal defect [103].

Physiologic RVH of the newborn is often impossible to distinguish from pathologic RVH without the aid of Vcg. An indication of pathologic RVH in the Vcg is the clockwise direction of inscription of the horizontal QRS loop as late as the age of 1—4 months [35, 52, 60, 80, 158, 188, 225].

Hypertrophy of the left heart (LVH) can also be established more reliably by Vcg than by scalar Ecg. Astvatsatrian examined 100 children with active rheumatic carditis and found that incipient LVH was revealed earlier by Vcg than by scalar Ecg [11]. The same finding was made by Massie and Walsh for mitral stenosis in 435 patients [146]. Eleven of 95 patients with congenital aortic stenosis had a normal scalar Ecg, but the Vcg revealed distinct signs of LVH in all but one of these cases [104]. Marini found that LVH was revealed better by Vcg than by scalar Ecg in 52 children with congenital aortic stenosis or rheumatic mitral insufficiency [145]. The Vcg finding has also been regarded as a very suitable criterion for following the disappearance of LVH after ductus arteriosus persistens surgery [194].

Donoso *et al.* discussed Vcg findings in both right and left ventricular hypertrophies and recorded typical findings [43]. The Vcg, Ecg and autopsy findings for 167 patients were compared by Wolff *et al.*, who were studying the possibilities of Vcg and scalar Ecg in the diagnosis of hypertrophy and they found Vcg to be essentially superior [245].

Vcg offers better chances than ordinary Ecg of demonstrating *combined hypertrophy* [48]. In cases of combined hypertrophy in infancy Elliott *et al.* established in the Vcg three different types which help in diagnosis that is sometimes difficult with ordinary electrocardiography [56]. The direction of inscription of the horizontal projection of the QRSsE loop is counter-clockwise in two types and forms a figure-of-eight in the third.

Vectorcardiographic findings in hypertrophies of ventricles have been extensively studied in very recent papers, too, and a good correlation has generally been established, although comparisons with scalar Ecg have usually been omitted since Vcg is now generally considered to give unquestionably superior results [36, 59 102, 103, 118, 122, 123, 133, 137 223, 230, 243].

Bundle branch blocks are elicited more reliably by Vcg than by scalar Ecg, especially partial bundle branch blocks. This was established for left bundle branch block [LBBB] by Pantridge et al. [161] and Scherlis and Grishman [205]. Richman and Wolff drew attention to the diagnostic difficulties that arise when right bundle branch block

[RBBB] imitates LBBB. If such cases are assessed according to Wilson criteria from ordinary Ecg curves, the two blocks are concomitant. The reason may be an especially vertical position of the heart or an infarction. Vcg gave better information in these cases than scalar Ecg. Most important from the diagnostic standpoint in such cases are the initial vectors. [183] Grishman pointed out the difficulty of distinguishing partial LBBB and RBBB from physiologic terminal delay and stated that Vcg helps in such cases to arrive at reliable diagnosis [78]

Lamer et al. analysed by means of Vcg the RSR' complex of scalar Ecg in right chest leads and reported that with Vcg it is easy to distinguish between RVH and RBBB [137] It was emphasized by Lamer and Grishman that diagnosis of LVH or myocardial disease is difficult if there is coincident right bundle branch block which causes deviation of the TsE loop to the left. However the configuration of the QRSsE loop in Vcg helps to give the correct diagnosis [131] Lamer and Grishman noted that Vcg makes it possible to differentiate between RVH and RBBB and Ecg changes caused by marked rotation of the heart [129, 130, 131]. Burch and DePasquale also emphasized the unreliability of scalar Ecg in the diagnosis of RBBB and obtained more reliable results by means of Vcg [21, 22]. Penaloza et al. [171] and Gamboa et al. [71] induced transient bundle branch block in the human heart by applying pressure to the interventricular septum. Their most important observation was that the QRS interval is not the only criterion in the diagnosis of bundle branch blocks; the morphology of the QRSsE loop is more important. The delay of the terminal appendage of the QRSsE loop may be completely absent in mild RBBB and the QRS interval may thus be normal in the Ecg. Eguchi et al. arrived at the same conclusion [50]. Consequently the earlier view that the rSR' pattern in lead V is suggestive of RVH alone without RBBB if the QRS interval is short can no longer be considered reliable.

In atrial septal defect of primum type Vcg yields highly characteristic finding [16, 22, 128, 143, 172] There are fairly typical Vcg findings in many other congenital heart defects, but the primum type ASD is the best example. Vectorcardiography has been employed widely to study also ventricular septal defects. Two very recent reports may be mentioned. The Vcg finding displayed a better correlation with hemodynamic changes than scalar Ecg in cases with ventricular septal defect [162] In 100 patients with ventricular septal defect a significant statistical correlation between the increased magnitude of the initial and maximum QRS vectorial forces and the degree of left-to-right shunt was established [115] The literature concerned with Vcg findings in connection with various congenital heart defects is already voluminous. Garcia-Palmieri et al. made a good summary of this subject [72]

Vectorcardiography is considered to be superior to scalar electrocardiography in myocardial infarction diagnosis. Findings have been presented in very many studies [23, 34, 112, 122, 148, 153, 205, 233, 242, 244]

Some authors have warned against exaggerating the diagnostic possibilities of Vcg [217] The necessity for epicardial, intracardial and esophageal leads to obtain more information than is given by electrodes placed on the skin surface has also been pointed out [124, 125] It must always be remembered that Ecg and Vcg are not alternative or competitive methods of studying the electrical activity of the heart; they must be employed parallelly Both of them have their own specific spheres of application.

In addition to actual vectorcardiographic diagnosis, the value of the vectorcardiographic method is that the experience it gives makes it easier to interpret an ordinary electrocardiogram and helps in understanding the origin and role of the changes seen in it. Vectorial thinking in the practical interpretation of ordinary scalar Ecg has been stressed especially by Jouve and Buisson [111].

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Table 2. The number of recordings made by different systems in the various age groups.

Age		Cube	Tetra-hedron	Helm	McFee and Parungao	Frank
0–12 hours	prematures					10
	full term infants					24
12–24 hours	prematures					10
	full term infants					20
24–48 hours	prematures					10
	full term infants	[illegible]	15	10	10	22
48–72 hours	prematures					10
	full term infants					25
3–4 days	prematures					15
	full term infants	15	17	10	10	40
7±1 days	prematures					29
	full term infants	22	20	10	15	45
14±1 days	prematures					25
	full term infants	20	20			[illegible]
21±1 days	prematures					15
	full term infants					28
28±1 days	prematures					15
	full term infants					15
Total		72	72	30	35	380

so, the type of murmur c) any other abnormal cardiac finding. In suspicious cases it was advised that the child should be taken to the cardiac outpatient department for examination. A reply was obtained in almost all the cases and only a few children had to be omitted from the material for lack of an answer. These measures were considered sufficient to prevent children with congenital heart disease from being included in the present series.

The children included in the material had no other known diseases that could affect cardiac function. On the other hand, they had diseases and symptoms such as dislocation of the hip, clubfoot, hydrocephalus, microcephalus, hemorrhagic disease, jaundice of varying etiology, symptoms of mild brain damage, suspicion of neonatal infection, congenital laryngeal stridor, vomiting, conjunctivitis, Pierre—Robin syndrome, status Bonnevie—Ullrich, cleft palate, cephalhematoma, torticollis and Erb's paresis. As regards jaundice and hemorrhagic disease, manifestly anemic patients were not included in the series. The prematures were generally hospitalised on account of their prematurity.

The recordings were done at the Children's Hospital of University of Turku, the Department of Pediatrics of University of Oulu and at the Obstetric Department of Abolands

3

PRESENT INVESTIGATION

MATERIAL AND METHOD

MATERIAL

The material consisted of 250 healthy newborn infants aged a few minutes to 28 days. Ninety of them were premature and 160 were born at term. The distribution of the birth weights is given in Table 1 Several records were usually made from the same infant, using one or several lead systems. Frank s system was the prin cipal method used, and thus a suffi cient number of records was obtained to analyse the development of the Vcg finding during the neonatal period. Recordings by the other systems were confined to a few age groups and the results were compared with those obtained by Frank s method. A total of 360 recordings were made by Frank s method. Their distribution into age groups is given in Table 2 which also shows the number of recordings performed by other methods and their age distribution. The total number of recordings was 569

Table 1 Birth weights of the infants.

Birth weight	Number of infants
1000 — 1500 g	14
1500 — 2000	33
2000 — 2500	43
2500 — 3000	30
3000 — 3500	52
3500 — 4000	44
4000 — 4500	28
4500 — 5000	6
Total	250

All the full term newborn were in good condition at birth and at the time of the recording. Their Apgar score at the age of 1 minute was 7—10 The prematures, especially the smallest, included newborn with a lower Apgar score and newborn who were weak but not actually asphyxiated at the time of the recording. Small prematures were in an incubator during the recording. None of the newborn studied had anything suggestive of heart disease in their history routine Ecg, auscultation finding or other clinical status. If there was the least suspicion, a chest roentgenogram was taken. As not all congenital heart defects show symptoms in the neonatal period, a questionnaire was sent to the mother of each child before he/she was a year old. The mother was asked to take the questionnaire with her to the child welfare centre for the more thorough examination performed at the age of one The welfare centre physician who made the examination filled in the question naire and returned it to the author The questionnaire covered the following points. a) whether a heart mur mur was heard on auscultation, b) if

T b1 2. The number of recordings made by different systems in the arious age groups.

Age		Cube	Tetrahedron	Halm	McFee and Parungao	Frank
0—12 hours	prematures					10
	full term infants					24
12—24 hours	prematures					10
	full term infants					20
24—48 hours	prematures					10
	full term infants	15	15	10	10	23
48—72 hours	prematures					10
	full term infants					25
3—4 days	prematures					15
	full term infants	15	[illegible]	10	10	40
7±1 days	prematures					28
	full term infants	22	20	10	15	45
14±1 days	prematures					25
	full term infants	20	20			15
21±1 days	prematures					15
	full term infants					15
28±1 days	prematures					15
	full term infants					15
Total		72	73	30	35	360

to the type of murmur c) any other abnormal cardiac finding. In suspicious cases it was advised that the child should be taken to the cardiac outpatient department for examination. A reply was obtained in almost all the cases and only a few children had to be omitted from the material for lack of an answer These measures were considered sufficient to prevent children with congenital heart disease from being included in the present series.

The children included in the material had no other known diseases that could affect cardiac function. On the other hand, they had diseases and symptoms such as dislocation of the hip, clubfoot, hydrocephalus, microcephalus, hemorrhagic disease jaundice of varying etiology symptoms of mild brain damage suspicion of neonatal infection, congenital laryngeal stridor vomiting, conjunctivitis, Pierre—Robin syndrome status Bonnevie—Ullrich, cleft palate cephalhematoma, torticollis and Erb s paresis. As regards jaundice and hemorrhagic disease, manifestly anemic patients were not included in the series. The prematures were generally hospitalized on account of their prematurity

The recordings were done at the Children s Hospital of University of Turku, the Department of Pediatrics of University of Oulu and at the Obstetric Department of Abolands

Sjukhus, Turku (a hospital owned by an association of communes) in 1963—1966. The following information was entered on cards for every patient.

1. Personal data, 2. Birth weight, birth length, head circumference and chest circumference immediately after birth 3. Age and weight at the time of recording, 4 Diagnosis, 5 History 6. Status, 7 Therapy 8. Mother's age and health 9 Course of the pregnancy 10 Course of the delivery 11. Apgar score 12. Data on siblings, 13 Familial diseases, 14. Anything else of note

None of the children in the series had received digitalis, sedatives or stimulants, corticosteroids or other drugs which might influence the function of the heart. During recording, the body temperature and the heart rate of every infant were within normal limits.

Most of the records were made halfway between meal times. Recording immediately before a meal is technically difficult on account of the restlessness of the infant. The infant is usually quiet on a full stomach, but the heart then lies slightly more horizontally than normal, which causes some deviation of the electrical axis of the heart to the left, at least in prematures [108] If the child was restless during the registration, he was given some time to settle and, if necessary an empty teat to suck. Sucking has an elevating effect on blood pressure from the second day of life in both full term infants and prematures [85 106] This, however is a finding that has been made on feeding the baby It is probable that sucking an empty comforter for pleasure when the child is not particularly hungry does not raise the blood pressure to the same extent. This possibility was considered by following the Vcg oscilloscopically before and after the baby was given the comforter and no difference was established.

APPARATUS

The electrocardiograph used for the recording was a two-channel Mingograph 24, made by Elema, Sweden. Both channels were connected to a two-channel oscilloscope Atlas Sichtgerät, made by Atlas, Germany The loops were photographed by a camera fixed at a standard distance from the tube The resistance-combining networks needed in Frank's and McFee's systems were prepared in the laboratory of the Cardiorespiratory Research Unit of Turku University Specially constructed electrodes, 1.0 cm in diameter were used and for the conductors thin, flexible hearing-aid wire. The electrodes were attached with breathing adhesive the electrodes around the thorax at the same level in Frank's system were fixed in position with a rubber belt. The large-sized electrodes used in Helm's system were made of rubber sponge and covered by rubber on the outer surface They were in five sizes, length of side 4.5—7.5 cm as it is important that the electrode size is in proper ratio to the patient's size. A broad rubber belt was used to fix these electrodes.

RECORDING TECHNIQUE

Vectorcardiographic recording is fairly sensitive to disturbances. Compared with ordinary electrocardiography this is because of the greater complexity of the method and the use of a five times greater amplitude which naturally amplifies the disturbances in the same ratio.

Newborn are exceptionally difficult examination objects for two reasons. Firstly the complete absence of co-operation and ready irritability on being woken and handled may make recording almost impossible in some cases. Secondly the skin resistance of the newborn is typically high. Measured between two electrodes the resistance varied from 50 K Ω to several thousand K Ω. High skin resistance places especially great requirements on the attachment of the electrodes. If the subject moves a good deal during the investigation it makes proper attachment still more difficult. In order to reduce skin resistance the infant's skin was wiped with a fatty solvent, usually an ether alcohol, before applying the electrodes. The resistance between the electrodes was the same when the electrode was applied as such to cleansed skin which had been moistened with physiological saline and when electrode paste or liquid was used. Mere physiological saline naturally dried more quickly. This was overcome by placing between the electrode and the skin a piece of blotting paper of the same diameter as the electrode, dipped in physiological saline. This method was employed in almost all the recordings; Elema's electrode paste was used in some. The inter electrode resistance was measured routinely. If the electrode-skin contact was faulty — an electrode often worked loose when the infant was restless — it was generally seen as an alternating current interference, or sometimes as a change in the loop configuration. It was sometimes difficult to eliminate an alternating current interference when recording in an incubator. For this reason, a Faraday cage with the dimensions of the incubator was made. Together with effective earthing it was sufficient on the whole to eliminate the disturbance. The disturbance eliminator of the electrocardiograph naturally cannot be used in vectorcardiography as the loop configuration and size change. When the finding differed perceptibly from the normal type a second recording was done after a short interval. There were hardly ever any great differences from the first record, which proves that the positioning of the electrodes was sufficiently constant.

If the patient was restless it was usually necessary to photograph several loops before a faultless and typical loop was obtained. This often required a fairly long time. The direction of inscription and the configuration of the loop were noted for every recording to avoid errors. Although the direction of inscription can be read from the parts of the broken line being traced that are sharp-pointed towards the direction of movement, there is a possibility of error when the configuration in a projection is intricate or comprises several loops.

Sjukhus, Turku (a hospital owned by an association of communes) in 1963—1968. The following information was entered on cards for every patient

1 Personal data, 2 Birth weight, birth length, head circumference and chest circumference immediately after birth, 3 Age and weight at the time of recording 4. Diagnosis, 5. History 6 Status, 7 Therapy 8. Mother's age and health, 9 Course of the pregnancy 10 Course of the delivery 11. Apgar score 12. Data on siblings, 13 Familial diseases, 14 Anything else of note

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by Simonson *et al.* [213] an arc-shaped protractor was used. When McFee's and Parungao's system was employed, the distances between the three precordial electrodes and that of the two electrodes in the left flank were reduced in relation to the patient's size (McFee and Parungao expressed the distances in centimetres for adults). It was generally not possible to make recordings by all five systems at the same time. One, two or three methods had to suffice and then the procedure was continued later. Five methods require too long a time when the subject is a newborn infant.

Frank's system proved to be obviously the best as the work progressed. It gave more uniform results, as will be seen later, and its practicalness made it slightly more advantageous than Helm's or McFee's and Parungao's systems. Accordingly it was later selected as the sole method. The collection of a large material by all five methods would have been pointless, in the author's opinion, in view of the enormous work that the recordings would require. All the recordings were performed and analysed by the author.

THE METHODS OF ANALYSIS OF THE RESULTS

The commonest targets of analysis in vectorcardiography were enumerated in the Review of the Literature (pages 25—29). The targets chosen for analysis in the present work were QRSsÊ half area vector, TsÊ half area vector, QRSsÊ polar vector, spatial QRS-T angle and 0.005 sec., 0.01 sec., 0.02 sec., 0.03 sec. and 0.04 sec. QRSsÊ instantaneous vectors. Models representing typical average QRS loops were drawn in each plane via the mean termini of the QRSsÊ instantaneous vectors.

Spatial QRSsÊ half area vector is not a fully absolute concept as the QRSsÊ loop is never completely in the so-called QRS plane. Using spatial rotation, it is possible to measure the half area vector of the projection of the QRSsÊ vector in this plane. This vector may be regarded as a spatial half area vector at least approximately. When the half area vector is determined without spatial rotation, the surface areas of the projections must be measured. But the half area vectors of different projections are by no means always *projections of the same vector*. Pipberger recommends *taking the temporal mean of the half* area vectors of all projections and *suggests* that vectors thus obtained be regarded as the projections of the spatial half area vector which corresponds to the true spatial mean vector [173]. This method is very inaccurate. It is much more accurate to determine the half area vector from the largest projection in its area. This was the method employed in the present study. The largest loop area is mostly in the sagittal projection, sometimes in the frontal projection, in the newborn. In the cases in which the area of the sagittal and frontal *projections* was roughly equal in size, *the half* area

For instance as the initial portion is sometimes traced counter-clockwise in the frontal projection, the direction of inscription is almost always ambiguous in the record because the initial loop is so small. Interpretation of the cardiograms is further complicated by the fact that the immediate vicinity of the 0 point is overexposed the luminous point lies in this area most of the exposure time since the PsE and TsE loops of the newborn are generally small and partly superimposed. In addition, the luminous point is immobile in the 0 point during the intervals between the inscription of the different loops. By drawing a sketch as accurate as possible while the loops are being recorded, and by comparing it with the cardiogram, it is possible to be sure that no errors originate in the direction of inscription and order of inscription of the different parts of complex loops.

Overexposure of the vicinity of the 0 point, to which reference was made above emerges much more clearly in an enlargement of the cardiogram than in the negative for the exposure margin of the former is only a fraction of that of the latter It was almost impossible to obtain decent records of Vcg loops in the enlargement. Consequently the following method was used With the negative in the projector an enlargement of the picture is projected onto white paper in a dark room. The recording is then drawn on the paper in conformity with the picture thrown by the projector and a simultaneous check is made against the sketch drawn at the time of recording It is possible in this way to obtain fully reliable, technically faultless and, thus, easily readable records even for the newborn. For each recording the calibration was also traced and drawn on paper in order to make the measurements reliable.

PsE loops were disregarded. They are the smallest and the most difficult to record. Consequently significant information is not often gained from them in the newborn.

Scalar curves were also made in each recording, using the same electrode placings. They may be indispensable in certain cases later to obtain a reliable idea of the result. They differed fairly often from the conventional Ecg curves of the same patients because the lead vectors are different.

LEAD SYSTEMS USED

In the early phase of the study five systems were used side by side Grishman s cube system [81] Wilson s tetrahedron system [238] Helm s system [91] McFee s and Parungao s system [150] and Frank s system [65] (pages 12—15) The last three are so-called corrected systems. With Frank s system, the thoracic electrodes were applied at the height of the 4th intercostal space since the infants were supine which is the general practice proven correct by e.g. Langner *et al.* [126] Aware of the great sensitiveness of the C electrode of Frank s system to localisation error which has also been shown experimentally since

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vectors of both were measured and their temporal mean was taken. The temporal values are then very close to one another or the same Once the timed vector in question has been determined the same timed vector is taken from other projections. They are the components of the spatial half area vector When a loop is much narrower in one projection than the others or is, say figure-of-eight in shape determination of its half area vector would not be of any use The determination of the spatial half area vector calls for careful delibera tion in special cases, e.g. if a part of the QRSsÊ loop deviates very much from the so-called QRS plane

The TsÊ loop is generally small and narrow and its *half area vector* is therefore visualised directly without measurement of the surface area. The newborn material included few cases with such a large TsÊ loop that it was advisable to measure the area of a projection planimetrically

A spatial resolver is generally used for the determination of *QRSsÊ polar vector* It makes it possible to examine a loop on its own plane and the spatial direction and length of the polar vector are readily revealed In the present work a simple method without a spatial resolver was used, as follows.

The directions of the spatial vectors are denoted by points on the surface of a sphere The projections of the instantaneous vectors on the planes are known. The spherical coordinates, azimuth and elevation, are determined by revolution [19] as shown in Fig. 5. All instantaneous vectors are marked by points on the spherical surface. A movable meridian is placed on them to determine the QRS plane The point determined by the axis of the polar vector on the spherical surface lies on the same degree of longitude as the lowest point of this mobile meridian and 90 degrees upwards of it. For control purposes, a movable meridian may also be placed perpendicularly to the above movable meridian and the point at which it intersects the above-mentioned longitudinal meridian can be fixed. The spherical coordinates of this point are noted.

The spatial direction of the polar vector has been determined in the above way Its length is directly proportional to the area of the spatial loop This has been calculated from the areas of the projections, which have been measured planimetrically

As mentioned earlier (page 27) there are several methods of determining the *spatial QRS T angle* In this study a very simple and accurate method was used. The spatial QRS-T angle is determined between the half area QRSsÊ and half area TsÊ vectors, since the half area vectors correspond best to the true mean vectors [173] Spatial half area vectors have already been determined for every loop. Their spherical coordinates are now determined by revolution and the axes of the vectors are marked by points on the surface

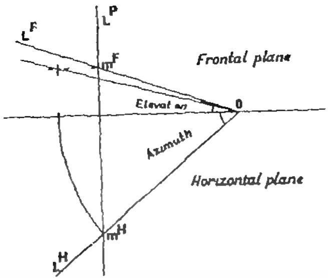

Fig. 6. Revolution when only the directions (L^F and L^H) of the vector projections are known. The azimuth is measured directly from the horizontal projection. An arbitrary perpendicular line (L^P) is plotted on the ground line some distance from the centre point O. Revolution is performed in the same way as in Fig. 5. by Om^F and Om^H, the parts of the projection lines bounded by the perpendicular line and the centre point.

of the sphere. The spatial angle between the QRSsÊ half area vector and TsÊ half area vector is then measured by a movable meridian. Brinberg's revolution method, described in Fig. 5 does not give an accurate determination of the spherical coordinates of TsÊ half area vector as the TsÊ loop is small. Vector lengths are of decisive importance in Brinberg's method, and thus the accuracy decreases when the vectors are small. In addition, it is sometimes difficult to make an accurate determination of the length of the TsÊ half area vector. Brinberg's revolution method was therefore modified in the present study: the vector lengths were dispensed with, and only their directions, the vector axes, were employed. An arbitrary perpendicular to the ground line was drawn to intersect their horizontal and frontal projections, and revolution was performed in the usual way by the segments of line bounded by this perpendicular and the 0 point (Fig. 6).

QRSsÊ instantaneous vectors were determined at intervals of 0.005—0.01 seconds. Since the loops are traced on the oscilloscope tube as a broken line — the breaks being 1/400 sec. — accurate temporal determination is possible. Instantaneous vectors are possible to determine at even shorter intervals if desired. The QRS interval was generally a little over 0.04 seconds, maximum 0.06 seconds, in the present material. A 0.04 second instantaneous vector was present in

practically all the QRSsE loops, but few QRS intervals were considerably longer than 0.05 seconds.

Reliable determination of QRSsE instantaneous vectors requires the combined examination of all their projections. The location of these vectors is often unclear from a single projection unless the examination is on the so-called QRS plane and even then difficulties may occur in many cases since some part of the loop may deviate appreciably from the plane. When a section of the loop runs perpendicularly to the plane temporal orientation at this site is impossible. When the path deviates considerably from the plane temporal orientation is difficult as the parts of the broken line are very short, especially if the inscription speed of the loop is slow in that section. An example of this is the 0 01 second vector which is often directed almost anteriorly It is then hardly possible to determine the frontal 0 01 second instantaneous QRS vector from a frontal projection alone On the other hand it is readily elicited by simultaneous examination of the sagittal projection, in which the 0 01 second instantaneous QRS vector is easy to determine The terminus of the frontal 0 01 second instantaneous QRS vector has naturally the same y component as the sagittal and is disclosed from the frontal projection by a point with the same y component. Similarly for each instantaneous vector it must be ensured that the projection of its terminus on every plane has roughly the same x, y and z coordinates.

STATISTICAL METHODS

There are certain difficulties involved in the statistical analysis of vectorcardiographic observations which do not occur in simple scalar quantities. Both vectorial and angular quantities have to be treated. The former are three-dimensional and have both direction and magnitude.

In the present work, the starting point of all the vectors was constant, the imaginary electrical centre of the heart. They can all be represented by *points determined by their termini in* the (x y z) coordinate system with its origo in the imaginary electrical centre of the heart. The projections of the points in question on the different planes, frontal, sagittal and horizontal, can be elicited in this way The spatial location of a point is established from its projections on two planes.

When analysing statistically a spatial vector group, its projections were always considered on two planes separately dealing with the x and y or y and z or z and x components of the points on each plane. As the standard deviation in the direction of two axes is hardly ever exactly the same the area of the standard deviation was drawn around the centre point as an ellipse with axes twice the length of the standard deviation parallel to both axes.

In the statistical treatment of angular quantities, Downs's method [46] which he and his co-workers recommended for vectorcardiography [47] and which was applied by Liebman *et al.* [139] for prematures, was not

used. This was because there was not in this material a deviation (range < 180 degrees) in angular quantities great enough to necessitate it.

Progressive changes occurred in some findings in the course of the investigation period. Regression analysis was planned, but the idea was abandoned because of the high number of different children in the various age groups. This was an inevitable consequence of the fact that a great proportion of the subjects were discharged from hospital during the investigation period and, also, the number in the youngest age groups was fairly small because of practical difficulties. In fact, the primary purpose was to investigate the possibility of applying the vectorcardiographic technique to the newborn and to establish normal findings for diagnostic use, rather than to follow the changes that occur during the neonatal period. Consequently these changes are presented in tabulated form or figures only giving the means and standard deviations.

For calculation of the arithmetic mean and the standard deviation, the sample was divided into classes, following the principle that the number of classes was to be the minimum of $^{2}\sqrt{n}$ where n refers to the total frequency of the sample.

The arithmetic mean was calculated from the following formula.

$$\bar{x} = \frac{1}{n} \sum_{i=1}^{k} n_i x_i$$

and *the standard deviation* from the formula

$$S = \sqrt{\frac{1}{n-1} \sum_{i=1}^{k} n_i (x_i - \bar{x})^2}$$

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where

$$s = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

where n_1 is the total frequency of x and n_2 that of y and s_1 is the standard deviation of x and s_2 the standard deviation of y. The t value thus obtained was compared with the values of Student's distribution table. If the risk (p) was

$0.01 < p < 0.05$	the difference between the means was called significant,
$0.0025 < p < 0.01$	the difference between the means was called highly significant,
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RESULTS

FRANK'S SYSTEM

Spatial QRSsÊ half area vector

Spatial QRSsÊ half area vectors were determined temporally according to the half area vector of the projection that was largest in area. The results are given in Figs. 7—9 where the projections of the termini of the vectors are in the frontal and horizontal planes. Sagittal projections were not given as they can be seen from the above. The frontal and horizontal projections were chosen because if one wishes to determine the spherical coordinates they are usually constructed from the frontal and horizontal projections by revolution.

It can be seen from the results in the frontal plane that the QRSsÊ half area vector tends to turn progressively to the left with age. Thus, this occurs in the neonatal period already but only to full-term newborn. The QRSsÊ half area vectors of prematures in the youngest age groups are situated more to the left than in full term infants and no significant progression of the kind mentioned occurs in prematures. This difference between premature and full term newborn has been previously established in many studies for the electrical axis of ordinary Ecg [190 192, 224] and also for Vcg in 24-hour old infants [139]. Fig. 10 shows the changing of the transverse component of the QRSsÊ half area vector in full-term infants.

In the horizontal projections, a change to the anterior direction in the QRSsÊ half area vectors was observed after the first week of life. Here we have another significant difference between premature and full-term newborn. The vectors of the prematures aged less than two weeks were distinctly more anterior and the difference was significant, except on the first day. Full term newborn displayed more shifting of the vectors to the anterior direction, and from the age of two weeks this difference was no longer demonstrable. The author has reported earlier on the more anterior location of the QRSsÊ half area vectors of prematures [107]. The changing of the sagittal component of the vectors in full-term newborn is illustrated in Fig. 11.

When turning to the left and anterior the QRSsÊ half area vectors assumed an increasingly vertical direction and were consequently grouped in the horizontal projection within a fairly short radius around the II point from the age of two weeks.

Spatial TsÊ half area vector

For the spatial TsÊ half area vectors only the spatial direction was determined. This was because it is dif

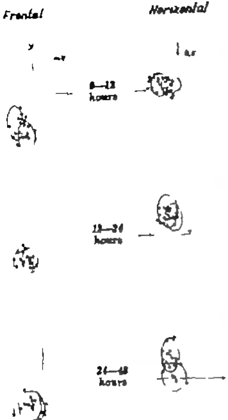


Fig. 7 Projections of the QRS&T half area vectors in the frontal and horizontal planes, age groups 0—12 hours, 12—24 hours and 24—48 hours. The solid dots indicate full-term infants and the circles prematures. The means of both are denoted by cross, for the latter in circle. The ellipse round both these crosses denotes the standard deviation in the direction of both axes.
The numerical values are:

0—12 hours
Full-term infants

Frontal	$\bar{x}$ = −0.263 mV	S_x = 0.117	$S(\bar{x})$ = 0.024	$S(S_x)$ = 0.016
	$\bar{y}$ = 0.387 mV	S_y = 0.224	$S(\bar{y})$ = 0.043	$S(S_y)$ = 0.034
Horiz.	$\bar{x}$ = −0.267 mV	S_x = 0.119	$S(\bar{x})$ = 0.017	$S(S_x)$ = 0.024
	$\bar{z}$ = −0.083 mV	S_z = 0.152	$S(\bar{z})$ = 0.032	$S(S_z)$ = 0.022

Prematures

Frontal	$\bar{x}$ = −0.120 mV	S_x = 0.125	$S(\bar{x})$ = 0.030	$S(S_x)$ = 0.026
	$\bar{y}$ = 0.390 mV	S_y = 0.303	$S(\bar{y})$ = 0.064	$S(S_y)$ = 0.045
Horiz.	$\bar{x}$ = −0.128 mV	S_x = 0.140	$S(\bar{x})$ = 0.044	$S(S_x)$ = 0.031
	$\bar{z}$ = −0.080 mV	S_z = 0.113	$S(\bar{z})$ = 0.036	$S(S_z)$ = 0.025

12—24 hours
Full-term infants

Frontal	$\bar{x}$ = −0.245 mV	S_x = 0.132	$S(\bar{x})$ = 0.042	$S(S_x)$ = 0.021
	$\bar{y}$ = 0.378 mV	S_y = 0.228	$S(\bar{y})$ = 0.051	$S(S_y)$ = 0.036
Horiz.	$\bar{x}$ = −0.225 mV	S_x = 0.141	$S(\bar{x})$ = 0.032	$S(S_x)$ = 0.022
	$\bar{z}$ = −0.225 mV	S_z = 0.220	$S(\bar{z})$ = 0.049	$S(S_z)$ = 0.035

Prematures

Frontal	$\bar{x}$ = −0.140 mV	S_x = 0.117	$S(\bar{x})$ = 0.037	$S(S_x)$ = 0.026
	$\bar{y}$ = 0.310 mV	S_y = 0.173	$S(\bar{y})$ = 0.055	$S(S_y)$ = 0.032
Horiz.	$\bar{x}$ = −0.140 mV	S_x = 0.117	$S(\bar{x})$ = 0.037	$S(S_x)$ = 0.026
	$\bar{z}$ = −0.230 mV	S_z = 0.130	$S(\bar{z})$ = 0.060	$S(S_z)$ = 0.043

24—48 hours
Full term infants

Frontal	$\bar{x}$ = −0.259 mV	S_x = 0.122	$S(\bar{x})$ = 0.026	$S(S_x)$ = 0.019
	$\bar{y}$ = 0.355 mV	S_y = 0.282	$S(\bar{y})$ = 0.036	$S(S_y)$ = 0.040
Horiz.	$\bar{x}$ = −0.259 mV	S_x = 0.120	$S(\bar{x})$ = 0.028	$S(S_x)$ = 0.020
	$\bar{z}$ = −0.246 mV	S_z = 0.246	$S(\bar{z})$ = 0.052	$S(S_z)$ = 0.037

Prematures

Frontal	$\bar{x}$ = −0.209 mV	S_x = 0.194	$S(\bar{x})$ = 0.062	$S(S_x)$ = 0.044
	$\bar{y}$ = 0.406 mV	S_y = 0.221	$S(\bar{y})$ = 0.070	$S(S_y)$ = 0.050
Horiz.	$\bar{x}$ = −0.219 mV	S_x = 0.186	$S(\bar{x})$ = 0.059	$S(S_x)$ = 0.042
	$\bar{z}$ = −0.016 mV	S_z = 0.197	$S(\bar{z})$ = 0.060	$S(S_z)$ = 0.044

FRANK'S SYSTEM

Spatial QRSsÊ half area vector

Spatial QRSsÊ half area vectors were determined temporally according to the half area vector of the projection that was largest in area. The results are given in Figs. 7—9 where the projections of the termini of the vectors are in the frontal and horizontal planes. Sagittal projections were not given as they can be seen from the above The frontal and horizontal projections were chosen because if one wishes to determine the spherical coordinates they are usually constructed from the frontal and horizontal projections by revolution.

It can be seen from the results in the frontal plane that the QRSsÊ half area vector tends to turn progressively to the left with age Thus, this occurs in the neonatal period already but *only to full term newborn.* The QRSsÊ half area vectors of prematures in the youngest age groups are situated more to the left than in full-term infants and no significant progression of the kind mentioned occurs in prematures. This difference between premature and full term newborn has been previously established in many studies for the electrical axis of ordinary Ecg [190 192, 224] and also for Vcg in 24-hour old infants [139] Fig 10 shows the changing of the transverse component of the QRSsÊ half area vector in full-term infants.

In the horizontal projections, a change to the anterior direction in the QRSsÊ half area vectors was observed after the first week of life. Here we have another significant difference between premature and full-term newborn. The vectors of the prematures aged less than two weeks were distinctly more anterior and the difference was significant, except on the first day Full-term newborn displayed more shifting of the vectors to the anterior direction, and from the age of two weeks this difference was no longer demonstrable. The author has reported earlier on the more anterior location of the QRSsÊ half area vectors of prematures [107] The changing of the sagittal component of the vectors in full term newborn is illustrated in Fig 11.

When turning to the left and anterior the QRSsÊ half area vectors assumed an increasingly vertical direction and were consequently grouped in the horizontal projection within a *fairly short radius* around the 0 point from the age of two weeks.

Spatial TsÊ half area vector

For the spatial TsÊ half area vectors only the spatial direction was determined. This was because it is dif

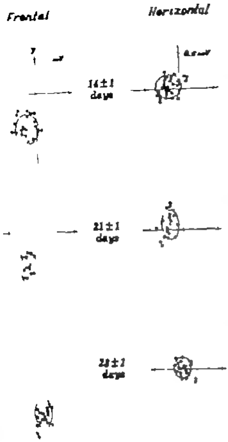


Fig. 9. Projections of the QRSaf half area vectors in the frontal and horizontal planes; age groups 14±1 days, 21±1 days and 28±1 days. For explanation, see Fig. 7

Numerical values:

14±1 days

Frontal	$\bar{x}$ = −0.160 mV	S_x = 0.176	$S(\bar{x})$ = 0.028	$S(S_x)$ = 0.020
	$\bar{y}$ = 0.503 mV	S_y = 0.214	$S(\bar{y})$ = 0.034	$S(S_y)$ = 0.024
Horiz.	$\bar{x}$ = −0.160 mV	S_x = 0.176	$S(\bar{x})$ = 0.028	$S(S_x)$ = 0.020
	$\bar{z}$ = −0.043 mV	S_z = 0.171	$S(\bar{z})$ = 0.027	$S(S_z)$ = 0.019

21±1 days

Frontal	$\bar{x}$ = −0.200 mV	S_x = 0.131	$S(\bar{x})$ = 0.024	$S(S_x)$ = 0.017
	$\bar{y}$ = 0.527 mV	S_y = 0.206	$S(\bar{y})$ = 0.038	$S(S_y)$ = 0.027
Horiz.	$\bar{x}$ = −0.197 mV	S_x = 0.132	$S(\bar{x})$ = 0.024	$S(S_x)$ = 0.017
	$\bar{z}$ = −0.073 mV	S_z = 0.206	$S(\bar{z})$ = 0.038	$S(S_z)$ = 0.027

28±1 days

Frontal	$\bar{x}$ = −0.087 mV	S_x = 0.121	$S(\bar{x})$ = 0.024	$S(S_x)$ = 0.017
	$\bar{y}$ = 0.523 mV	S_y = 0.205	$S(\bar{y})$ = 0.038	$S(S_y)$ = 0.027
Horiz.	$\bar{x}$ = −0.090 mV	S_x = 0.132	$S(\bar{x})$ = 0.024	$S(S_x)$ = 0.017
	$\bar{z}$ = −0.010 mV	S_z = 0.152	$S(\bar{z})$ = 0.038	$S(S_z)$ = 0.020

ficult to determine their length accurately since they are fairly short and the measurement is complicated by the instability of the 0 point of the newborn and the over-exposure of its immediate environment in the photograph. In the newborn it is the orientation of the Taf loop that is of primary importance in practical analysis and diagnosis. The other properties of the T wave and also of the S-T segment are visualised better in an ordinary scalar Ecg.

The directions of the spatial Taf half area vectors are given in Fig. 12. Similarly to the QRSaf half area vectors, only their frontal and horizontal projections are entered in the figure. If required, the spherical coordinates can be determined from them by revolution (Fig. 8). The spherical coordinates have not been entered here as the plane projections are more important for practical analysis and diagnosis. Because of the definite skewness of the deviation of the findings, the arithmetic mean and standard deviation were not calculated. It seems that Taf half area vectors tend to assume a downward and slightly left

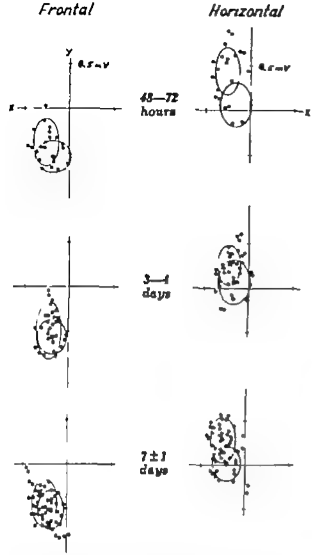


Fig. 8. Projections of the QRSaß half area vectors in the frontal and horizontal planes, age groups 48—72 hours, 3—4 days and 7±1 days. For explanation, see fig 7

Numerical values:

48—72 hours
Full term infants

Frontal $\bar{x}$	= −0.252 mV	$\bar{y}$	= 0.392 mV
S_x	= 0.134	S_y	= 0.285
$S(\bar{x})$	= 0.027	$S(\bar{y})$	= 0.057
$S(S_x)$	= 0.019	$S(S_y)$	= 0.040
Horiz. $\bar{x}$	= −0.256 mV	$\bar{z}$	= −0.436 mV
S	= 0.126	S_z	= 0.268
$S(\bar{x})$	= 0.025	$S(\bar{z})$	= 0.053
$S(S_x)$	= 0.018	$S(S_z)$	= 0.038

Prematures

Frontal $\bar{x}$	= −0.178 mV	$\bar{y}$	= 0.550 mV
S_x	= 0.190	S_y	= 0.184
$S(\bar{x})$	= 0.060	$S(\bar{y})$	= 0.058
$S(S_x)$	= 0.043	$S(S_y)$	= 0.041
Horiz. $\bar{x}$	= −0.166 mV	$\bar{z}$	= −0.050 mV
S_x	= 0.177	S_z	= 0.246
$S(\bar{x})$	= 0.057	$S(\bar{z})$	= 0.078
$S(S_x)$	= 0.040	$S(S_z)$	= 0.055

3—4 days
Full term infants

Frontal $\bar{x}$	= −0.218 mV	$\bar{y}$	= 0.490 mV
S_x	= 0.135	S_y	= 0.330
$S(\bar{x})$	= 0.021	$S(\bar{y})$	= 0.052
$S(S_x)$	= 0.015	$S(S_y)$	= 0.037
Horiz. $\bar{x}$	= −0.220 mV	$\bar{z}$	= −0.257 mV
S_x	= 0.124	S_z	= 0.236
$S(\bar{x})$	= 0.020	$S(\bar{z})$	= 0.037
$S(S_x)$	= 0.014	$S(S_z)$	= 0.026

Prematures

Frontal $\bar{x}$	= −0.183 mV	$\bar{y}$	= 0.563 mV
S_x	= 0.173	S_y	= 0.190
$S(\bar{x})$	= 0.043	$S(\bar{y})$	= 0.048
$S(S_x)$	= 0.031	$S(S_y)$	= 0.034
Horiz. $\bar{x}$	= −0.167 mV	$\bar{z}$	= −0.073 mV
S_x	= 0.184	S_z	= 0.260
$S(\bar{x})$	= 0.048	$S(\bar{z})$	= 0.067
$S(S_x)$	= 0.034	$S(S_z)$	= 0.047

7±1 days
Full term infants

Frontal $\bar{x}$	= −0.259 mV	$\bar{y}$	= 0.448 mV
S_x	= 0.148	S_y	= 0.267
$S(\bar{x})$	= 0.022	$S(\bar{y})$	= 0.040
$S(S_x)$	= 0.016	$S(S_y)$	= 0.029
Horiz. $\bar{x}$	= −0.264 mV	$\bar{z}$	= −0.291 mV
S_x	= 0.143	S_z	= 0.271
$S(\bar{x})$	= 0.021	$S(\bar{z})$	= 0.039
$S(S_x)$	= 0.015	$S(S_z)$	= 0.029

Prematures

Frontal $\bar{x}$	= −0.177 mV	$\bar{y}$	= 0.527 mV
S_x	= 0.150	S_y	= 0.224
$S(\bar{x})$	= 0.027	$S(\bar{y})$	= 0.041
$S(S_x)$	= 0.019	$S(S_y)$	= 0.029
Horiz. $\bar{x}$	= −0.224 mV	$\bar{z}$	= −0.014 mV
S_x	= 0.163	S_z	= 0.194
$S(\bar{x})$	= 0.030	$S(\bar{z})$	= 0.034
$S(S_x)$	= 0.021	$S(S_z)$	= 0.025

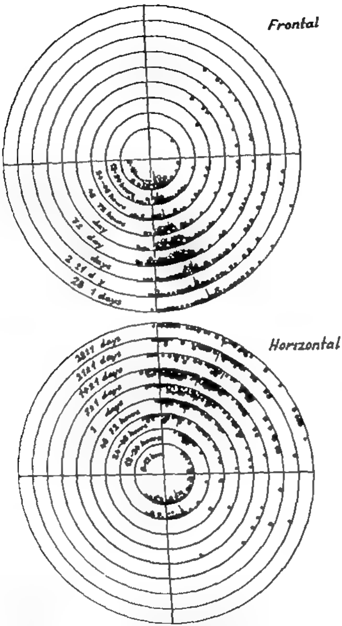


Fig 12 Directions of the frontal and horizontal projections of the Taft half area vectors. The solid dots indicate full term and the circles premature infants. The medians are marked by lines parallel to the radius.

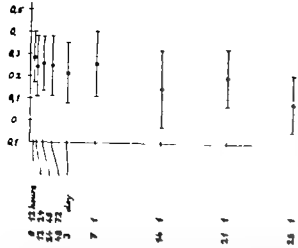


Fig. 10. Transverse components of the QRSsÊ half area vectors for full term infants according to age groups. The standard deviation on both sides of the mean is indicated.

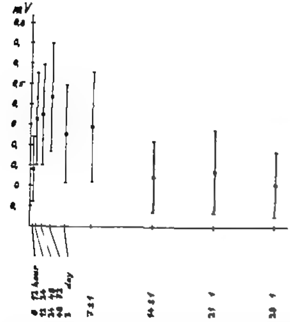


Fig. 11. Sagittal components of the QRSsÊ half area vectors for full term infants according to age groups. The standard deviation on both sides of the mean is indicated.

ward and posterior direction. Some of the vectors are directed sharply to the left, in some cases even slightly superiorly or anteriorly. On the other hand only a few vectors are directed to the right, and even those very slightly being located close to the centre of the clustering. As the arithmetic mean in such a case would lead to a false conclusion, a median was calculated for each age group. The medians were entered in the figure by lines parallel to the radius.

It can be seen from Fig. 12 that the direction of the TsÊ half area vectors gradually tends to shift to the left on moving to the older age groups, although the differences are not great. The typical changes in the first day of life emerge clearly. However all the vectors are then not located on the positive side of the axis of the conventional V_1 lead. Few recordings made during the first few minutes of the infant's life are included. Hait and Casul [84] reported that the TsÊ loop is then on the negative side of the axis of the V_1 lead and only afterwards assumes the typical first-day orientation. The same thing happened in the few infants of the present series for which a recording was made during the first minutes of life. However no concentration on the finding during these first minutes of the infant's life was made since it is not associated with the actual aim of this work and it is very difficult to get reliable Vcg recordings so rapidly. Conventional scalar Ecg is more suitable when the recording has to be performed in a couple of minutes.

No differences in the direction of the TsÊ vectors were established between premature and full-term newborn.

Table 5. Spatial QRS-T angles.

Age	Prematures		Full-term infants	
	Mean	SD	Mean	SD
0—12 hours	37.2°	27.0°	53.3	28.7°
12—24	50.7	25.2	56.8°	28.0°
24—48	61.0°	22.7	63.1	22.8
48—72	57.4	24.4	52.7°	23.1
3—4 days	52.6	24.5°	45.1	22.6°
7±1	45.1	23.9°	41.2°	24.4
14±1	42.8°	24.6	44.6°	21.3
21±1	38.1	22.4	42.5	17.1
28±1	37.2°	19.7°	35.8	12.6

planar QRS-T angles are not important (see p. 77) they were not determined at all. Because the dispersion of the values was not very great, the angles were treated as scalar quantities in the calculation of the means and standard deviations.

It has been established that the spatial QRS-T angle is widest in the neonatal period [12, 94] and that its deviation is greatest in the youngest infants [60]. The spatial QRS-T angles obtained in this study were distinctly smaller throughout than in the materials mentioned. A slight narrowing tendency seemed to appear in the course of the neonatal period, except that the angle was surprisingly small in prematures aged under 12 hours. However the dispersion was great in this group and such a limited number of cases does not warrant any conclusions. No significant parallel differences were seen between premature and full-term newborn, although the values for the prematures were higher in most age groups. The dispersion was also generally a little higher for the prematures.

QRSsÊ instantaneous vectors and configuration of the QRSsÊ loop

The 0.01, 0.02, 0.03 and 0.04 second instantaneous vectors were determined from all the recordings. The results are shown in *Figs.* 13—21. The 0.005 second initial vector was also determined and its *x* component is given in Fig. 22.

The means and standard deviations were calculated for the planar projections of the groups of spots formed by the termini of the instantaneous vectors. This was done by calculating them for the projections of these spots on the x, y z coordinates. Loops were drawn through the midpoints of the groups of spots. These loops run between the spots in the same way as on an average and can consequently be considered to represent the typical loops for the age groups in question.

Two progressive changes seen distinctly in these records occur during the neonatal period. Firstly there is a typical change *in the horizontal projection* from the fairly oval loops of the youngest age groups, with their clockwise direction of inscription, to slightly narrower loops which, in the typical cases, form a figure-of-eight where the direction of inscription of the anterior part is counter-clockwise. This development *resembles* in some degree that reported by Elek *et al.* [52] but differs considerably in that there were also posterior potentials in the present work. The types introduced by Elek and his co-workers had no posterior potentials, their loops were

QRSsÊ polar vector

The axes of the spherical coordinates determined for the QRSsÊ polar vectors are given in Table 3. The areas of the spatial QRSsÊ loops which decide the lengths of the polar vectors are listed in Table 4 where the value 1.0 is given to the median of the largest group infants aged 7±1 days. The arithmetic mean and standard deviation were not calculated here because they would give a false impression due to the skewness of the dispersion. When the axial directions of polar vectors are presented on a spherical surface, their lengths are directly proportional to the area of the spot displaying each vector.

Table 3. Spherical coordinates of the QRSsÊ polar vectors.

Age	Azimuth		Elevation	
	Mean	SD	Mean	SD
0—12 hours	—33.2	30.3	+20.3	23.3
12—24	—24.7	29.4	+24.4	28.9
24—48	—25.1	32.8	+20.2	20.8
48—72	—29.2	31.9	+19.3	21.8
3—4 days	—31.0	33.0	+16.9	30.2
7±1	—28.3	32.6*	+15.2*	28.3
14±1	—32.6	35.4	+13.7	26.7
21±1	—29.8*	33.5	+14.4	32.1
28±1	—27.2*	30.5	+10.0	24.0*

Table 4. Surface areas of the spatial QRSsÊ loops. *The value 1.00 has been given to the median of the 7±1 days age group, which is the largest one.*

	Median	Range
0—12 hours	1.25	0.48—3.45
12—24	1.22	0.45—3.12
24—48	1.15	0.41—3.23
48—72	1.13	0.21—3.33
3—4 days	0.97	0.24—3.28
7±1	1.00	0.21—3.40
14±1	1.18	0.29—3.36
21±1	1.21	0.19—2.98
28±1	1.38	0.25—3.31

No great progressive changes occurred with age in the direction of the polar vectors. The only significant change was the slight reduction in elevation of them during the neonatal period. The QRSsÊ loop then moves to a nearly vertical position. No definite differences were established between premature and full-term newborn.

The lengths of the polar vectors remained practically the same until the age of 3 weeks and was somewhat higher at 4 weeks (Table 4).

The polar vector cannot be determined with full exactitude because the QRSsÊ loop is not completely in the same plane and determination of this QRS plane is always a little uncertain. This difficulty is greater than usual in the newborn since the tortuosity is greater. In the present study the initial potentials deviated fairly noticeably from the QRS plane in nearly all the cases, but there were other fairly great deviations as well. It seems in fact that the polar vector is perhaps not quite as useful a quantity for characterising the loops for the newborn as it is later in life. But as increased tortuosity causes inaccuracy even in all the other objects of analysis, the polar vector deserves its place.

Spatial QRS-T angle

The magnitudes of the spatial QRS-T angle are given in Table 5. As the

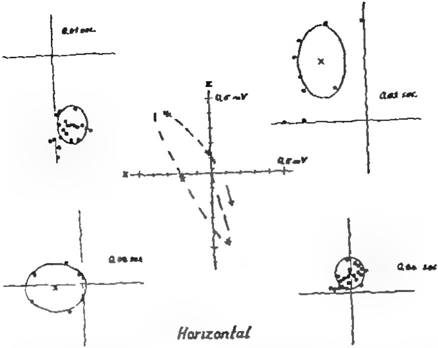


Fig. 11. Projections of the QRS instantaneous vectors in different planes and the typical loops drawn in their mean value points for infants aged 6—12 hours. The solid dots indicate full-term and the circles premature infants. Crosses indicate the means. The ellipses around them indicate the standard deviation separately for the direction of both axes. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
x	= 0.132	y	= 0.021	z	= 0.015	y	= 0.008	x	= 0.115	z	= 0.488
S_x	= 0.120	S_y	= 0.101	S_z	= 0.103	S_y	= 0.093	S_x	= 0.118	S_z	= 0.120
$S(x)$	= 0.032	$S(y)$	= 0.017	$S(z)$	= 0.018	$S(y)$	= 0.018	$S(x)$	= 0.019	$S(z)$	= 0.022
$S(S_x)$	= 0.015	$S(S_y)$	= 0.012	$S(S_z)$	= 0.012	$S(S_y)$	= 0.011	$S(S_x)$	= 0.013	$S(S_z)$	= 0.018

0.02 sec.

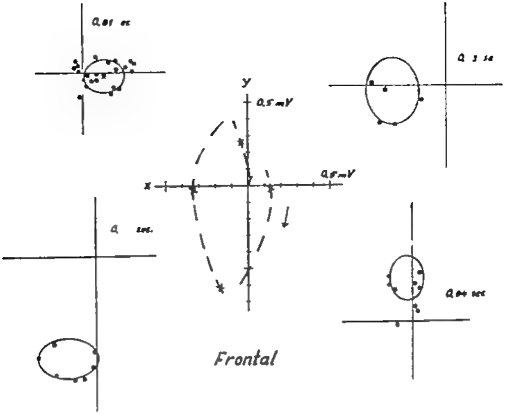
Frontal				Right sagittal				Horizontal			
x	= −0.109	y	= 0.017	z	= 0.024	y	= 0.009	x	= −0.200	z	= 0.028
S_x	= 0.190	S_y	= 0.123	S_z	= 0.150	S_y	= 0.129	S_x	= 0.218	S_z	= 0.183
$S(x)$	= 0.032	$S(y)$	= 0.021	$S(z)$	= 0.028	$S(y)$	= 0.022	$S(x)$	= 0.036	$S(z)$	= 0.027
$S(S_x)$	= 0.022	$S(S_y)$	= 0.013	$S(S_z)$	= 0.018	$S(S_y)$	= 0.018	$S(S_x)$	= 0.025	$S(S_z)$	= 0.019

0.03 sec.

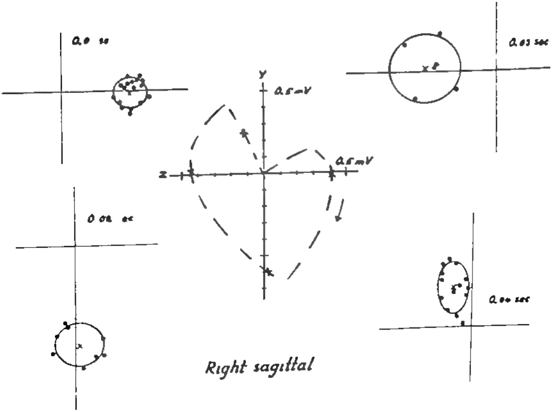
Frontal				Right sagittal				Horizontal			
x	= −0.332	y	= 0.027	z	= −0.444	y	−0.015	x	= −0.283	z	= −0.403
S_x	= 0.170	S_y	= 0.205	S_z	= 0.218	S_y	= 0.212	S_x	= 0.154	S_z	= 0.246
$S(x)$	= 0.029	$S(y)$	= 0.033	$S(z)$	= 0.037	$S(y)$	= 0.036	$S(x)$	= 0.025	$S(z)$	= 0.042
$S(S_x)$	= 0.021	$S(S_y)$	= 0.043	$S(S_z)$	= 0.028	$S(S_y)$	= 0.026	$S(S_x)$	= 0.019	$S(S_z)$	= 0.030

0.04 sec.

Frontal				Right sagittal				Horizontal			
x	= −0.036	y	= −0.259	z	= −0.118	y	= −0.250	x	= −0.012	z	= −0.134
S_x	= 0.075	S_y	= 0.136	S_z	= 0.094	S_y	= 0.108	S_x	= 0.095	S_z	= 0.099
$S(x)$	= 0.022	$S(y)$	= 0.015	$S(z)$	= 0.016	$S(y)$	= 0.029	$S(x)$	= 0.018	$S(z)$	= 0.017
$S(S_x)$	= 0.014	$S(S_y)$	= 0.024	$S(S_z)$	= 0.011	$S(S_y)$	= [illegible]	$S(S_x)$	= 0.012	$S(S_z)$	= 0.012



Frontal



Right sagittal

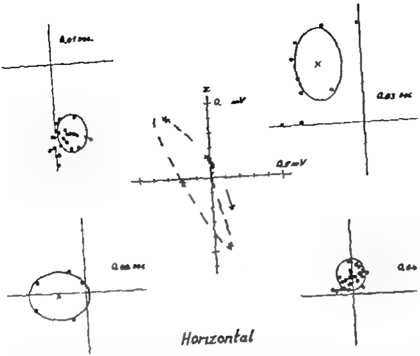
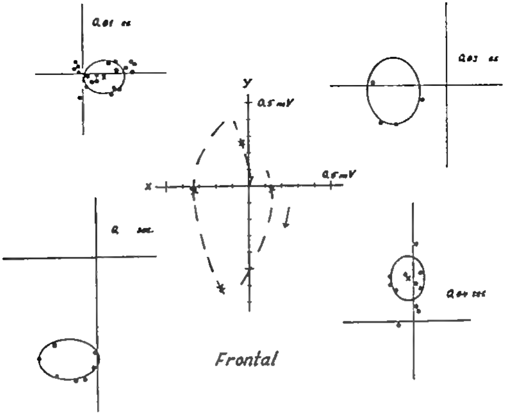
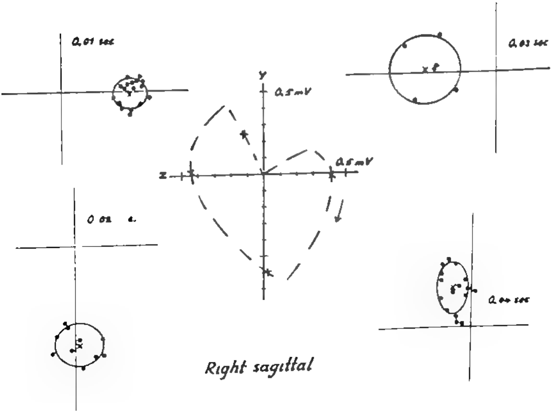


Fig. 13. Projections of the QRS-∂ instantaneous vectors in different planes and the typical loops drawn via their mean value points for infants aged 0—12 hours. The solid dots indicate full term and the circles premature infants. Crosses indicate the means. The ellipses around them indicate the standard deviation separately for the direction of both axes. Numerical values: (mV)

	Frontal				Right sagittal				Horizontal			
0.01 sec.												
	x	= 0.133	y	= 0.021	z	= 0.415	y	= 0.009	x	= 0.115	z	= 0.468
	S_x	= 0.120	S_y	= 0.161	S_z	= 0.103	S_y	= 0.092	S_x	= 0.110	S_z	= 0.130
	$S(x)$	= 0.022	$S(y)$	= 0.017	$S(z)$	= 0.018	$S(y)$	= 0.016	$S(x)$	= 0.019	$S(z)$	= 0.022
	$S(S_x)$	= 0.015	$S(S_y)$	= 0.012	$S(S_z)$	= 0.012	$S(S_y)$	= 0.011	$S(S_x)$	= 0.013	$S(S_z)$	= 0.016
0.02 sec.												
	x	= −0.169	y	= 0.617	z	= 0.024	y	= 0.609	x	= −0.200	z	= 0.028
	S_x	= 0.190	S_y	= 0.123	S_z	= 0.150	S_y	= 0.129	S_x	= 0.216	S_z	= 0.163
	$S(x)$	= 0.032	$S(y)$	= 0.021	$S(z)$	= 0.026	$S(y)$	= 0.022	$S(x)$	= 0.036	$S(z)$	= 0.027
	$S(S_x)$	= 0.022	$S(S_y)$	= 0.015	$S(S_z)$	= 0.018	$S(S_y)$	= 0.016	$S(S_x)$	= 0.025	$S(S_z)$	= 0.019
0.03 sec.												
	x	= −0.332	y	= 0.027	z	= −0.444	y	= −0.015	x	= −0.285	z	= −0.403
	S_x	= 0.178	S_y	= 0.205	S_z	= 0.216	S_y	= 0.212	S_x	= 0.154	S_z	= 0.246
	$S(x)$	= 0.028	$S(y)$	= 0.035	$S(z)$	= 0.037	$S(y)$	= 0.036	$S(x)$	= 0.028	$S(z)$	= 0.042
	$S(S_x)$	= 0.021	$S(S_y)$	= 0.043	$S(S_z)$	= 0.026	$S(S_y)$	= 0.026	$S(S_x)$	= 0.019	$S(S_z)$	= 0.030
0.04 sec.												
	x	= −0.036	y	= −0.208	z	= −0.118	y	= −0.258	x	= −0.012	z	= −0.234
	S_x	= 0.975	S_y	= 0.156	S_z	= 0.094	S_y	= 0.168	S_x	= 0.095	S_z	= 0.099
	$S(x)$	= 0.022	$S(y)$	= 0.015	$S(z)$	= 0.016	$S(y)$	= 0.029	$S(x)$	= 0.016	$S(z)$	= 0.017
	$S(S_x)$	= 0.014	$S(S_y)$	= 0.024	$S(S_z)$	= 0.011	$S(S_y)$	= 0.020	$S(S_x)$	= 0.012	$S(S_z)$	= 0.012



Frontal



Right sagittal

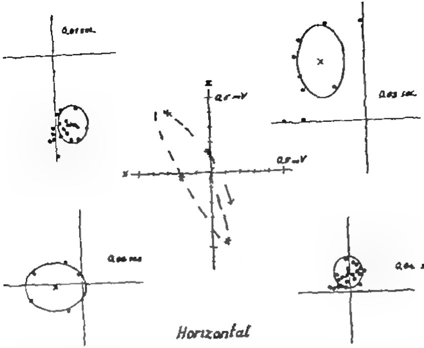


Fig. 12. Projections of the QRS&T instantaneous vectors in different planes and the typical loops drawn via their mean value points for infants aged 0—12 hours. The solid dots indicate full term and the circles premature infants. Crosses indicate the means. The ellipses around them indicate the standard deviation separately for the direction of both axes. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
x	= 0.133	y	= 0.021	z	= 0.415	y	= 0.009	x	= 0.115	z	= 0.468
S_x	= 0.130	S_y	= 0.101	S_z	= 0.103	S_y	= 0.092	S_x	= 0.110	S_z	= 0.136
$S(x)$	= 0.023	$S(y)$	= 0.017	$S(z)$	= 0.018	$S(y)$	= 0.018	$S(x)$	= 0.019	$S(z)$	= 0.022
$S(S_x)$	= 0.015	$S(S_y)$	= 0.013	$S(S_z)$	= 0.012	$S(S_y)$	= 0.011	$S(S_x)$	= 0.013	$S(S_z)$	= 0.016

0.02 sec.

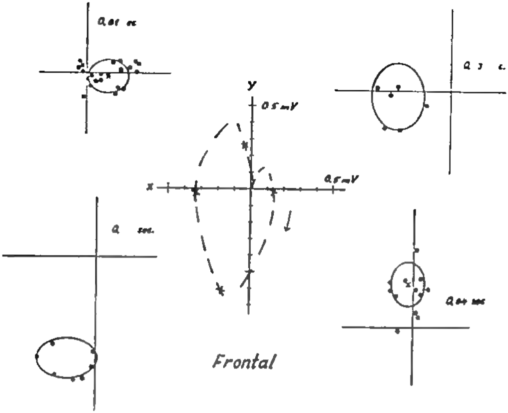
Frontal				Right sagittal				Horizontal			
x	= −0.189	y	= 0.017	z	= 0.024	y	= 0.009	x	= −0.200	z	= 0.028
S_x	= 0.190	S_y	= 0.133	S_z	= 0.130	S_y	= 0.129	S_x	= 0.218	S_z	= 0.183
$S(x)$	= 0.032	$S(y)$	= 0.021	$S(z)$	= 0.026	$S(y)$	= 0.022	$S(x)$	= 0.036	$S(z)$	= 0.027
$S(S_x)$	= 0.022	$S(S_y)$	= 0.013	$S(S_z)$	= 0.018	$S(S_y)$	= 0.016	$S(S_x)$	= 0.025	$S(S_z)$	= 0.019

0.03 sec.

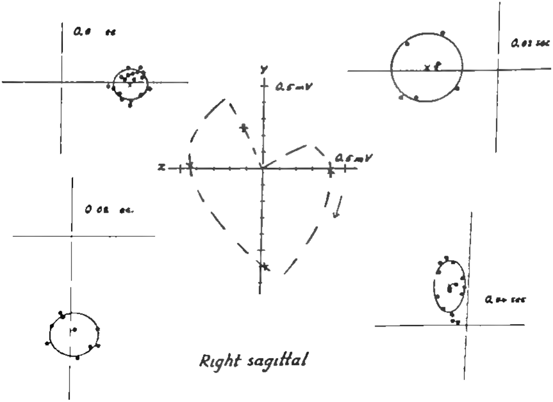
Frontal				Right sagittal				Horizontal			
x	= −0.332	y	= 0.027	z	= −0.444	y	= −0.815	x	= −0.265	z	= −0.403
S_x	= 0.170	S_y	= 0.205	S_z	= 0.218	S_y	= 0.212	S_x	= 0.154	S_z	= 0.248
$S(x)$	= 0.029	$S(y)$	= 0.035	$S(z)$	= 0.037	$S(y)$	= 0.026	$S(x)$	= 0.026	$S(z)$	= 0.042
$S(S_x)$	= 0.021	$S(S_y)$	= 0.015	$S(S_z)$	= 0.028	$S(S_y)$	= 0.026	$S(S_x)$	= 0.019	$S(S_z)$	= 0.030

0.04 sec.

Frontal				Right sagittal				Horizontal			
x	= −0.938	y	= −0.262	z	= −0.228	y	= −0.256	x	= −0.012	z	= −0.134
S_x	= 0.973	S_y	= 0.136	S_z	= 0.084	S_y	= 0.168	S_x	= 0.095	S_z	= 0.090
$S(x)$	= 0.022	$S(y)$	= 0.033	$S(z)$	= 0.018	$S(y)$	= 0.029	$S(x)$	= 0.016	$S(z)$	= 0.017
$S(S_x)$	= 0.014	$S(S_y)$	= 0.024	$S(S_z)$	= 0.011	$S(S_y)$	= 0.020	$S(S_x)$	= 0.012	$S(S_z)$	= 0.012



Frontal



Right sagittal

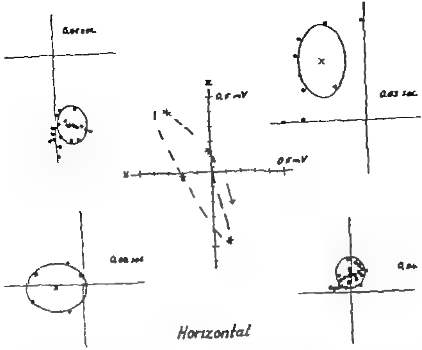


Fig. 13. Projections of the QRS-loop instantaneous vectors in different planes and the typical loops drawn via their mean value points for infants aged 0—12 hours. The solid dots indicate full-term and the circles premature infants. Crosses indicate the means. The ellipses around them indicate the standard deviation separately for the direction of both axes. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
x	= 0.128	y	= 0.021	z	= 0.415	y	= 0.009	x	= 0.115	z	= 0.486
S_x	= 0.120	S_y	= 0.101	S_z	= 0.103	S_y	= 0.092	S_x	= 0.110	S_z	= 0.130
$S(x)$	= 0.022	$S(y)$	= 0.017	$S(z)$	= 0.016	$S(y)$	= 0.016	$S(x)$	= 0.019	$S(z)$	= 0.022
$S(S_x)$	= 0.015	$S(S_y)$	= 0.012	$S(S_z)$	= 0.012	$S(S_y)$	= 0.011	$S(S_x)$	= 0.013	$S(S_z)$	= 0.016

0.02 sec.

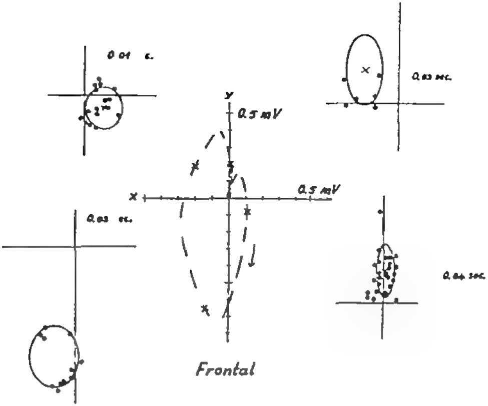
Frontal				Right sagittal				Horizontal			
	= −0.160	y	= 0.017	z	= 0.024	y	= 0.009	x	= −0.200	z	= 0.028
S_x	= 0.160	S_y	= 0.123	S_z	= 0.159	S_y	= 0.129	S_x	= 0.216	S_z	= 0.163
$S(x)$	= 0.032	$S(y)$	= 0.021	$S(z)$	= 0.026	$S(y)$	= 0.022	$S(x)$	= 0.036	$S(z)$	= 0.027
$S(S_x)$	= 0.022	$S(S_y)$	= 0.015	$S(S_z)$	= 0.018	$S(S_y)$	= 0.016	$S(S_x)$	= 0.025	$S(S_z)$	= 0.019

0.03 sec.

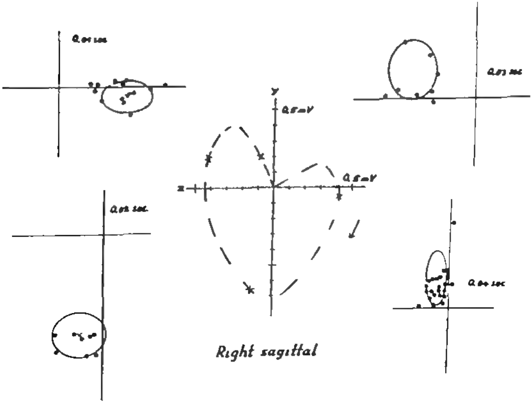
Frontal				Right sagittal				Horizontal			
	= −0.332	y	= 0.027	z	= −0.444	y	= −0.015	x	= −0.285	z	= −0.403
S_x	= 0.170	S_y	= 0.205	S_z	= 0.216	S_y	= 0.212	S_x	= 0.154	S_z	= 0.246
$S(x)$	= 0.029	$S(y)$	= 0.033	$S(z)$	= 0.037	$S(y)$	= 0.036	$S(x)$	= 0.026	$S(z)$	= 0.042
$S(S_x)$	= 0.021	$S(S_y)$	= 0.045	$S(S_z)$	= 0.026	$S(S_y)$	= 0.026	$S(S_x)$	= 0.019	$S(S_z)$	= 0.030

0.04 sec.

Frontal				Right sagittal				Horizontal			
x	= −0.036	y	= −0.268	z	= −0.118	y	= −0.268	x	= −0.013	z	= −0.134
S_x	= 0.073	S_y	= 0.136	S_z	= 0.094	S_y	= 0.186	S_x	= 0.065	S_z	= 0.089
$S(x)$	= 0.022	$S(y)$	= 0.035	$S(z)$	= 0.016	$S(y)$	= 0.029	$S(x)$	= 0.016	$S(z)$	= 0.017
$S(S_x)$	= 0.014	$S(S_y)$	= 0.024	$S(S_z)$	= 0.011	$S(S_y)$	= 0.030	$S(S_x)$	= 0.012	$S(S_z)$	= 0.012



Frontal



Right sagittal

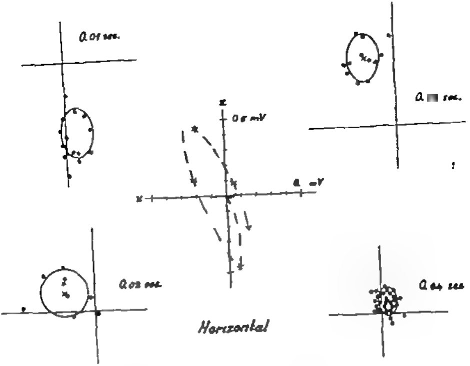


Fig. 14 Projections of the QRS⊕ instantaneous vectors in different planes and the typical loops for infants aged 12—24 hours. For explanation, see Fig. 13. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
X	= 0.080	Y	= 0.070	Z	= 0.420	Y	= 0.057	X	= 0.080	Z	= 0.475
S_x	= 0.106	S_y	= 0.109	S_z	= 0.154	S_y	= 0.100	S_x	= 0.105	S_z	= 0.150
S(X)	= 0.013	S(Y)	= 0.020	S(Z)	= 0.028	S(Y)	= 0.018	S(X)	= 0.019	S(Z)	= 0.029
$S(S_x)$	= 0.014	$S(S_y)$	= 0.014	$S(S_z)$	= 0.020	$S(S_y)$	= 0.012	$S(S_x)$	= 0.013	$S(S_z)$	= 0.029

0.02 sec.

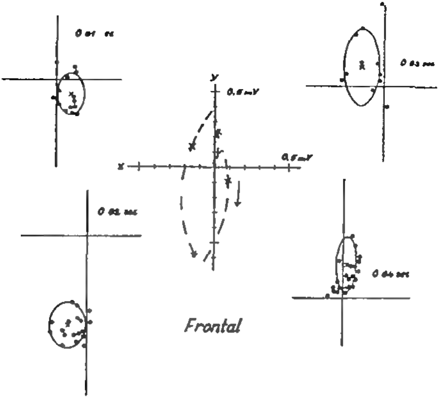
Frontal				Right sagittal				Horizontal			
X	= −0.130	Y	= 0.653	Z	= −0.150	Y	= 0.524	X	= −0.207	Z	= −0.123
S_x	= 0.144	S_y	= 0.167	S_z	= 0.106	S_y	= 0.143	S_x	= 0.153	S_z	= 0.155
S(X)	= 0.026	S(Y)	= 0.031	S(Z)	= 0.030	S(Y)	= 0.026	S(X)	= 0.030	S(Z)	= 0.028
$S(S_x)$	= 0.018	$S(S_y)$	= 0.021	$S(S_z)$	= 0.021	$S(S_y)$	= 0.019	$S(S_x)$	= 0.021	$S(S_z)$	= 0.020

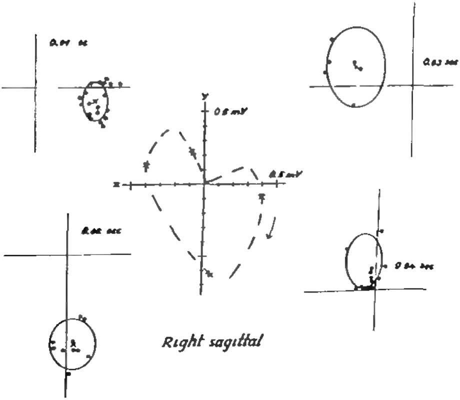
0.03 sec.

Frontal				Right sagittal				Horizontal			
	−0.203	Y	= −0.197	Z	= −0.418	Y	= −0.180	X	= −0.205	Z	= −0.450
S_x	0.103	S_y	= 0.203	S_z	= 0.139	S_y	= 0.138	S_x	= 0.106	S_z	= 0.161
S(X)	0.019	S(Y)	= 0.037	S(Z)	= 0.041	S(Y)	= 0.048	S(X)	= 0.019	S(Z)	= 0.029
$S(S_x)$	0.013	$S(S_y)$	= 0.026	$S(S_z)$	= 0.029	$S(S_y)$	= 0.034	$S(S_x)$	= 0.014	$S(S_z)$	= 0.021

0.04 sec.

Frontal				Right sagittal				Horizontal			
X	= 0.008	Y	= −0.201	Z	= −0.060	Y	= −0.187	X	= 0.040	Z	= −0.078
S_x	0.052	S_y	= 0.157	S_z	= 0.060	S_y	= 0.168	S_x	= 0.062	S_z	= 0.074
S(X)	= 0.009	S(Y)	= 0.029	S(Z)	= 0.011	S(Y)	= 0.030	S(X)	= 0.011	S(Z)	= 0.013
$S(S_x)$	0.006	$S(S_y)$	= 0.020	$S(S_z)$	= 0.008	$S(S_y)$	= 0.021	$S(S_x)$	= 0.008	$S(S_z)$	= 0.009


0.01 sec
0.02 sec
0.03 sec
0.04 sec
0.5 mV
0.5 mV
X
Y
Frontal


0.01 sec
0.02 sec
0.03 sec
0.04 sec
0.5 mV
0.5 mV
X
Y
Right sagittal

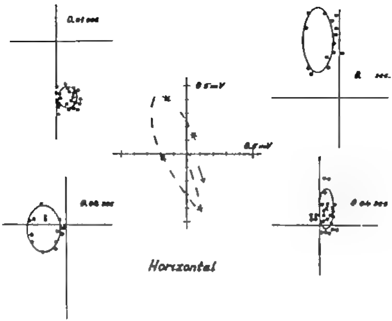


Fig. 15 Projections of the QRSaR instantaneous vectors in different planes and the typical loops for infants aged 24—48 hours. For explanation, see Fig. 13. Numerical values: (mV)

Frontal

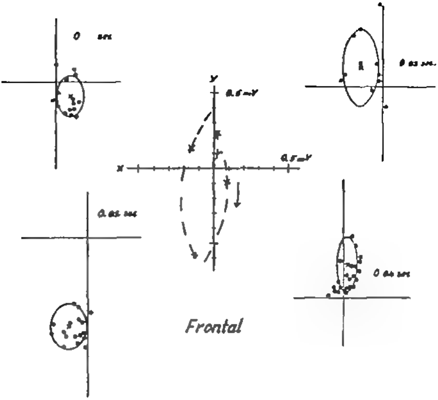
	X	S_x	$S(X)$	$S(S_x)$	Y	S_y	$S(Y)$	$S(S_y)$
0.01 sec.	0.080	0.061	0.011	0.015	0.097	0.135	0.025	0.017
0.02 sec.	−0.128	0.123	0.022	0.015	0.680	0.151	0.027	0.019
0.03 sec.	−0.147	0.114	0.021	0.018	−0.127	0.261	0.048	0.034
0.04 sec.	0.027	0.068	0.013	0.009	−0.228	0.181	0.035	0.025

Right sagittal

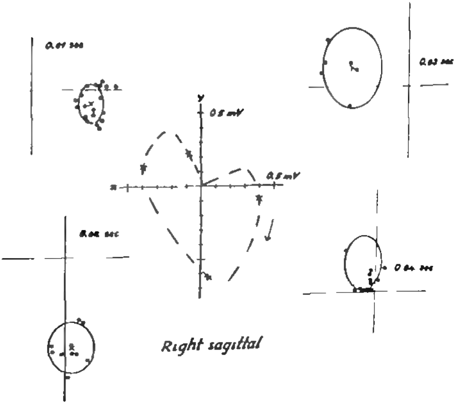
	Z	S_z	$S(Z)$	$S(S_z)$	Y	S_y	$S(Y)$	$S(S_y)$
0.01 sec.	0.409	0.098	0.016	0.011	0.097	0.125	0.025	0.018
0.02 sec.	0.040	0.138	0.029	0.021	0.630	0.172	0.031	0.022
0.03 sec.	−0.390	0.197	0.035	0.025	−0.132	0.251	0.045	0.032
0.04 sec.	−0.080	0.127	0.023	0.016	−0.217	0.130	0.024	0.025

Horizontal

	X	S_x	$S(X)$	$S(S_x)$	Z	S_z	$S(Z)$	$S(S_z)$
0.01 sec.	0.098	0.073	0.013	0.009	0.412	0.078	0.014	0.018
0.02 sec.	−0.182	0.128	0.022	0.016	0.033	0.164	0.028	0.020
0.03 sec.	−0.153	0.113	0.021	0.015	−0.410	0.232	0.041	0.029
0.04 sec.	[illegible]	0.043	0.011	0.008	−0.123	0.142	0.025	0.017



Frontal



Right sagittal

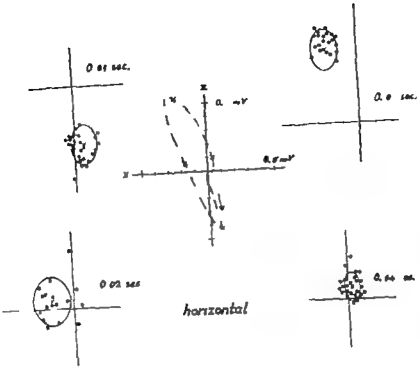
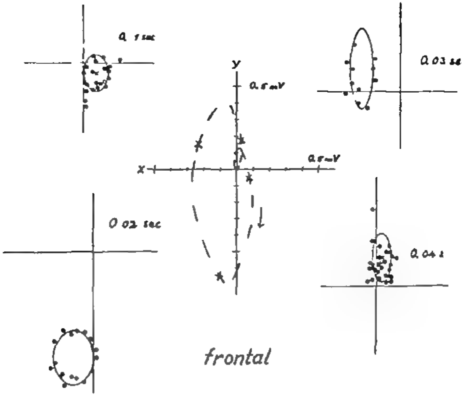
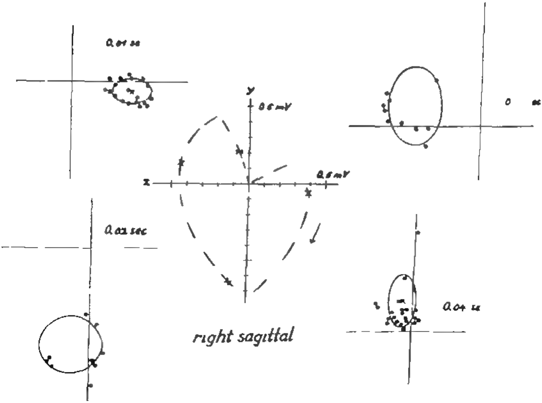


Fig. 14. Projections of the QRSaE instantaneous vectors in different planes and the typical loops for infants aged 48—72 hours. For explanation, see Fig. 12. Numerical values: (mV)

Frontal		Right sagittal		Horizontal	
0.01 sec.		**0.01 sec.**		**0.01 sec.**	
$x = 0.088$	$y = 0.080$	$z = 0.106$	$y = 0.600$	$x = 0.078$	$z = 0.429$
$S_x = 0.074$	$S_y = 0.118$	$S_z = 0.112$	$S_y = 0.088$	$S_x = 0.099$	$S_z = 0.140$
$S(x) = 0.012$	$S(y) = 0.019$	$S(z) = 0.020$	$S(y) = 0.015$	$S(x) = 0.018$	$S(z) = 0.024$
$S(S_x) = 0.008$	$S(S_y) = 0.013$	$S(S_z) = 0.014$	$S(S_y) = 0.010$	$S(S_x) = 0.012$	$S(S_z) = 0.016$
0.02 sec.		**0.02 sec.**		**0.02 sec.**	
$x = -0.106$	$y = 0.849$	$z = -0.103$	$y = 0.647$	$x = -0.154$	$z = -0.060$
$S_x = 0.124$	$S_y = 0.178$	$S_z = 0.198$	$S_y = 0.179$	$S_x = 0.145$	$S_z = 0.179$
$S(x) = 0.021$	$S(y) = 0.028$	$S(z) = 0.033$	$S(y) = 0.030$	$S(x) = 0.024$	$S(z) = 0.030$
$S(S_x) = 0.013$	$S(S_y) = 0.020$	$S(S_z) = 0.024$	$S(S_y) = 0.021$	$S(S_x) = 0.017$	$S(S_z) = 0.021$
0.03 sec.		**0.03 sec.**		**0.03 sec.**	
$x = -0.225$	$y = -0.109$	$z = -0.435$	$y = -0.140$	$x = -0.232$	$z = -0.540$
$S_x = 0.067$	$S_y = 0.245$	$S_z = 0.181$	$S_y = 0.253$	$S_x = 0.081$	$S_z = 0.154$
$S(x) = 0.012$	$S(y) = 0.041$	$S(z) = 0.031$	$S(y) = 0.043$	$S(x) = 0.015$	$S(z) = 0.026$
$S(S_x) = 0.008$	$S(S_y) = 0.029$	$S(S_z) = 0.022$	$S(S_y) = 0.031$	$S(S_x) = 0.011$	$S(S_z) = 0.018$
0.04 sec.		**0.04 sec.**		**0.04 sec.**	
$x = 0.032$	$y = -0.171$	$z = -0.067$	$y = -0.202$	$x = 0.031$	$z = -0.090$
$S_x = 0.057$	$S_y = 0.154$	$S_z = 0.193$	$S_y = 0.180$	$S_x = 0.064$	$S_z = 0.109$
$S(x) = 0.009$	$S(y) = 0.026$	$S(z) = 0.015$	$S(y) = 0.030$	$S(x) = 0.010$	$S(z) = 0.018$
$S(S_x) = 0.007$	$S(S_y) = 0.018$	$S(S_z) = 0.011$	$S(S_y) = 0.021$	$S(S_x) = 0.007$	$S(S_z) = 0.013$



frontal



right sagittal

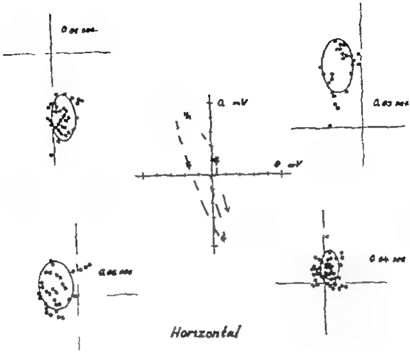


Fig. 17 Projections of the QRSaT instantaneous vectors in different planes and the typical loops for infants aged 3—4 days. For explanation, see Fig. 13. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
x	0.062	y	0.024	z	0.401	y	0.021	x	0.063	z	0.462
S_x	0.062	S_y	0.116	S_z	0.176	S_y	0.111	S_x	0.090	S_z	[illegible]
$S(x)$	0.011	$S(y)$	0.016	$S(z)$	0.024	$S(y)$	0.015	$S(x)$	0.012	$S(z)$	0.021
$S(S_x)$	0.008	$S(S_y)$	0.011	$S(S_z)$	0.017	$S(S_y)$	0.011	$S(S_x)$	0.008	$S(S_z)$	0.015

0.02 sec.

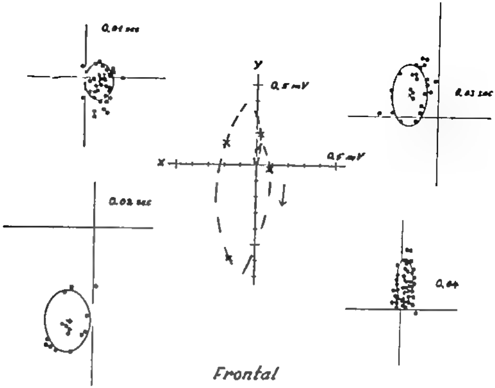
Frontal				Right sagittal				Horizontal			
x	−0.153	y	0.560	z	−0.043	y	[illegible]	x	−0.186	z	−0.064
S_x	0.145	S_y	0.397	S_z	0.138	S_y	0.177	S_x	0.133	S_z	0.171
$S(x)$	0.020	$S(y)$	0.021	$S(z)$	0.018	$S(y)$	0.023	$S(x)$	0.018	$S(z)$	0.022
$S(S_x)$	0.014	$S(S_y)$	0.019	$S(S_z)$	0.013	$S(S_y)$	0.016	$S(S_x)$	0.013	$S(S_z)$	0.017

0.03 sec.

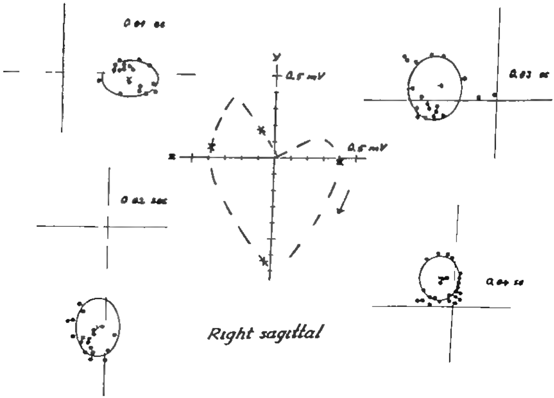
Frontal				Right sagittal				Horizontal			
x	−0.184	y	−0.133	z	−0.286	y	−0.073	x	−0.188	z	−0.42[illegible]
S_x	0.105	S_y	0.193	S_z	0.162	S_y	0.124	S_x	0.110	S_z	0.18[illegible]
$S(x)$	0.014	$S(y)$	0.026	$S(z)$	0.022	$S(y)$	0.026	$S(x)$	0.015	$S(z)$	0.02[illegible]
$S(S_x)$	0.010	$S(S_y)$	0.018	$S(S_z)$	0.015	$S(S_y)$	0.019	$S(S_x)$	0.010	$S(S_z)$	0.011

0.04 sec.

Frontal				Right sagittal				Horizontal			
x	0.025	y	−0.019	z	−0.087	y	−0.178	x	0.027	z	−0.103
S_x	0.059	S_y	0.136	S_z	0.120	S_y	0.134	S_x	0.065	S_z	0.115
$S(x)$	0.008	$S(y)$	0.018	$S(z)$	0.017	$S(y)$	0.018	$S(x)$	0.009	$S(z)$	0.015
$S(S_x)$	0.006	$S(S_y)$	0.013	$S(S_z)$	0.012	$S(S_y)$	0.012	$S(S_x)$	0.006	$S(S_z)$	0.011



Frontal



Right sagittal

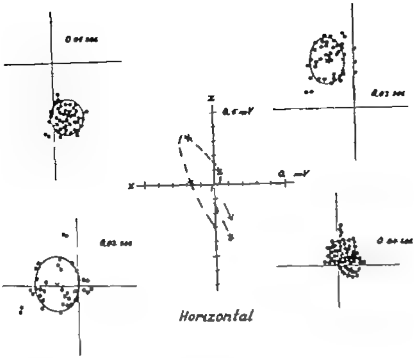


Fig. 12. Projections of the QRSaE instantaneous vectors in different planes and the typical loops for infants aged 7±1 days. For explanation, see Fig. 11. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
x	= 0.118	y	= 0.032	z	= 0.354	y	= 0.036	x	= 0.110	z	= 0.378
S_x	= 0.086	S_y	= 0.139	S_z	= 0.115	S_y	= 0.124	S_x	= 0.117	S_z	= 0.124
S(x)	= 0.018	S(y)	= 0.016	S(z)	= 0.013	S(y)	= 0.016	S(x)	= 0.014	S(z)	= 0.014
$S(S_x)$	= 0.007	$S(S_y)$	= 0.013	$S(S_z)$	= 0.009	$S(S_y)$	= 0.011	$S(S_x)$	= 0.010	$S(S_z)$	= 0.010

0.02 sec.

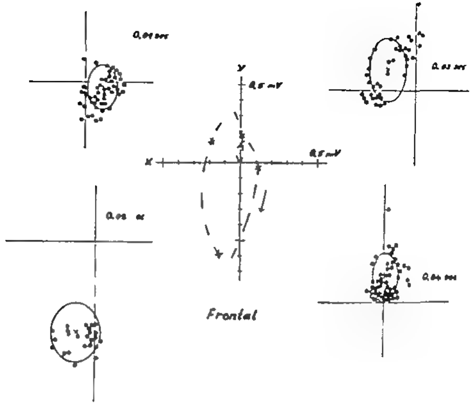
Frontal				Right sagittal				Horizontal			
x	= −0.133	y	= 0.102	z	= −0.016	y	= 0.039	x	= −0.137	z	= −0.004
S_x	= 0.134	S_y	= 0.194	S_z	= 0.177	S_y	= 0.194	S_x	= 0.163	S_z	= 0.190
S(x)	= 0.018	S(y)	= 0.023	S(z)	= 0.020	S(y)	= 0.022	S(x)	= 0.019	S(z)	= 0.022
$S(S_x)$	= 0.013	$S(S_y)$	= 0.016	$S(S_z)$	= 0.014	$S(S_y)$	= 0.016	$S(S_x)$	= 0.014	$S(S_z)$	= 0.016

0.03 sec.

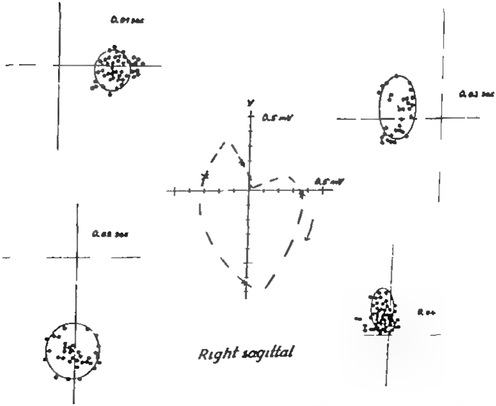
Frontal				Right sagittal				Horizontal			
x	= −0.188	y	= −0.139	z	= −0.301	y	= −0.095	x	= −0.188	z	= −0.316
S_x	= 0.117	S_y	= 0.203	S_z	= 0.128	S_y	= 0.218	S_x	= 0.124	S_z	= 0.164
S(x)	= 0.014	S(y)	= 0.023	S(z)	= 0.015	S(y)	= 0.025	S(x)	= 0.014	S(z)	= 0.018
$S(S_x)$	= 0.010	$S(S_y)$	= 0.017	$S(S_z)$	= 0.010	$S(S_y)$	= 0.018	$S(S_x)$	= 0.010	$S(S_z)$	= 0.013

0.04 sec.

Frontal				Right sagittal				Horizontal			
x	= 0.009	y	= −0.170	z	= −0.057	y	= −0.184	x	= 0.037	z	= −0.078
S_x	= 0.083	S_y	= 0.148	S_z	= 0.075	S_y	= 0.142	S_x	= 0.090	S_z	= 0.097
S(x)	= 0.004	S(y)	= 0.017	S(z)	= 0.008	S(y)	= 0.017	S(x)	= 0.010	S(z)	= 0.011
$S(S_x)$	= 0.003	$S(S_y)$	= 0.012	$S(S_z)$	= 0.006	$S(S_y)$	= 0.012	$S(S_x)$	= 0.007	$S(S_z)$	= 0.008



Frontal



Right sagittal

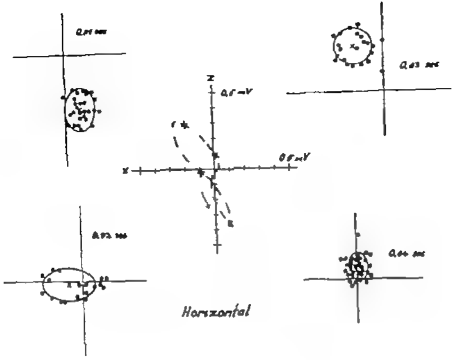


Fig. 19 Projections of the QRSaE instantaneous vectors in different planes and the typical loops for infants aged 14±1 days. For explanation, see Fig. 13. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
$\bar{x}$	= 0.100	$\bar{y}$	= −0.015	$\bar{z}$	= 0.243	$\bar{y}$	= −0.016	$\bar{x}$	= 0.091	$\bar{z}$	= 0.255
S_x	= 0.088	S_y	= 0.060	S_z	= 0.145	S_y	= 0.063	S_x	= 0.098	S_z	= 0.128
$S(\bar{x})$	= 0.014	$S(\bar{y})$	= 0.013	$S(\bar{z})$	= 0.023	$S(\bar{y})$	= 0.014	$S(\bar{x})$	= 0.015	$S(\bar{z})$	= 0.022
$S(S_x)$	= 0.010	$S(S_y)$	= 0.009	$S(S_z)$	= 0.017	$S(S_y)$	= 0.010	$S(S_x)$	= 0.011	$S(S_z)$	= 0.016

0.02 sec.

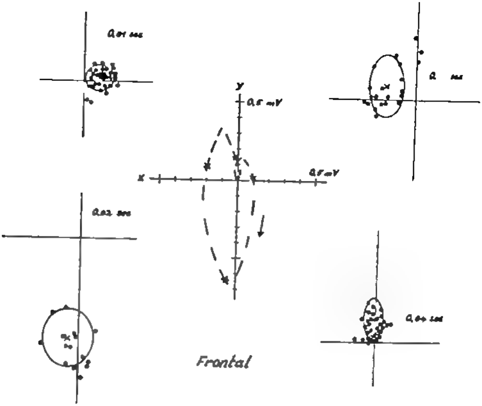
Frontal				Right sagittal				Horizontal			
$\bar{x}$	= −0.064	$\bar{y}$	= 0.645	$\bar{z}$	= 0.256	$\bar{y}$	= 0.605	$\bar{x}$	= −0.100	$\bar{z}$	= 0.013
S_x	= 0.161	S_y	= 0.192	S_z	= 0.118	S_y	= 0.190	S_x	= 0.182	S_z	= 0.116
$S(\bar{x})$	= 0.025	$S(\bar{y})$	= 0.030	$S(\bar{z})$	= 0.018	$S(\bar{y})$	= 0.023	$S(\bar{x})$	= 0.029	$S(\bar{z})$	= 0.017
$S(S_x)$	= 0.018	$S(S_y)$	= 0.021	$S(S_z)$	= 0.013	$S(S_y)$	= 0.016	$S(S_x)$	= 0.020	$S(S_z)$	= 0.012

0.03 sec.

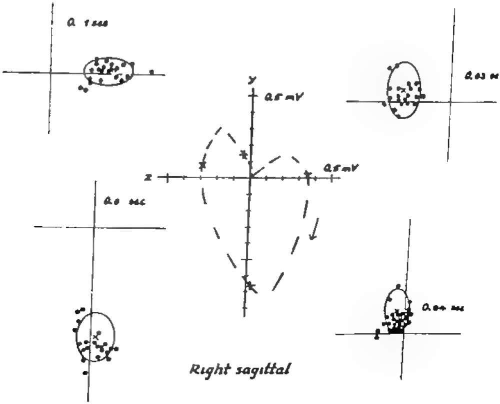
Frontal				Right sagittal				Horizontal			
$\bar{x}$	= −0.186	$\bar{y}$	= −0.074	$\bar{z}$	= −0.297	$\bar{y}$	= −0.065	$\bar{x}$	= −0.195	$\bar{z}$	= −0.297
S_x	= 0.116	S_y	= 0.200	S_z	= 0.100	S_y	= 0.168	S_x	= 0.127	S_z	= 0.112
$S(\bar{x})$	= 0.019	$S(\bar{y})$	= 0.032	$S(\bar{z})$	= 0.016	$S(\bar{y})$	= 0.027	$S(\bar{x})$	= 0.021	$S(\bar{z})$	= 0.018
$S(S_x)$	= 0.013	$S(S_y)$	= 0.022	$S(S_z)$	= 0.011	$S(S_y)$	= 0.019	$S(S_x)$	= 0.015	$S(S_z)$	= 0.013

0.04 sec.

Frontal				Right sagittal				Horizontal			
$\bar{x}$	= −0.012	$\bar{y}$	= −0.154	$\bar{z}$	= −0.051	$\bar{y}$	= −0.141	$\bar{x}$	= 0.068	$\bar{z}$	= −0.063
S_x	= 0.063	S_y	= 0.135	S_z	= 0.070	S_y	= 0.135	S_x	= 0.061	S_z	= 0.063
$S(\bar{x})$	= 0.017	$S(\bar{y})$	= 0.021	$S(\bar{z})$	= 0.011	$S(\bar{y})$	= 0.021	$S(\bar{x})$	= 0.010	$S(\bar{z})$	= 0.013
$S(S_x)$	= 0.010	$S(S_y)$	= 0.015	$S(S_z)$	= 0.008	$S(S_y)$	= 0.015	$S(S_x)$	= 0.007	$S(S_z)$	= 0.009



Frontal



Right sagittal

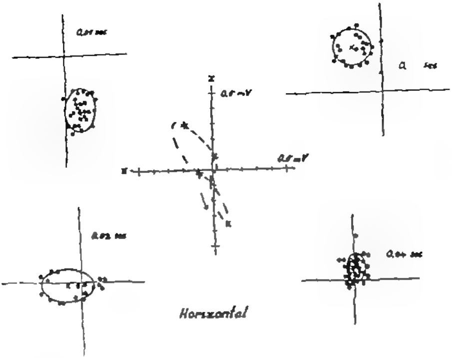


Fig. 19 Projections of the QRS&T instantaneous vectors in different planes and the typical loops for infants aged 14±1 days. For explanation, see Fig. 12. Numerical values: (mV)

0.01 sec.

Frontal				Right sagittal				Horizontal			
X	= 0.108	Y	= −0.013	Z	= 0.243	Y	= −0.016	X	= 0.081	Z	= 0.253
S_x	= 0.088	S_y	= 0.080	S_z	= 0.143	S_y	= [illegible]	S_x	= 0.098	S_z	= 0.128
S(x)	= 0.014	S(y)	= 0.013	S(z)	= 0.023	S(y)	= [illegible]	S(x)	= 0.015	S(z)	= 0.022
$S(S_x)$	= 0.010	$S(S_y)$	= 0.009	$S(S_z)$	= 0.017	$S(S_y)$	= 0.016	$S(S_x)$	= 0.011	$S(S_z)$	= 0.015

0.02 sec.

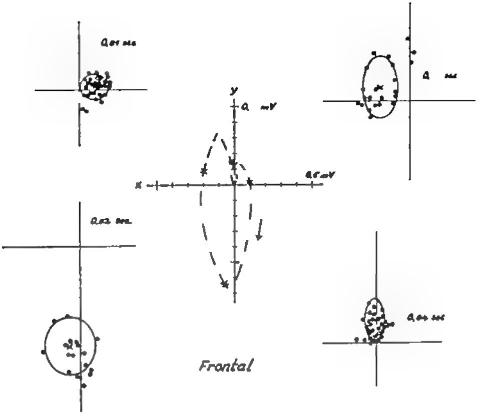
Frontal				Right sagittal				Horizontal			
X	= −0.064	Y	= 0.045	Z	= 0.258	Y	= 0.443	X	= −0.100	Z	= 0.013
S_x	= 0.161	S_y	= 0.182	S_z	= 0.118	S_y	= 0.139	S_x	= 0.182	S_z	= 0.110
S(x)	= 0.025	S(y)	= 0.030	S(z)	= 0.018	S(y)	= 0.022	S(x)	= 0.029	S(z)	= 0.017
$S(S_x)$	= 0.018	$S(S_y)$	= 0.021	$S(S_z)$	= 0.013	$S(S_y)$	= 0.016	$S(S_x)$	= 0.020	$S(S_z)$	= 0.012

0.03 sec.

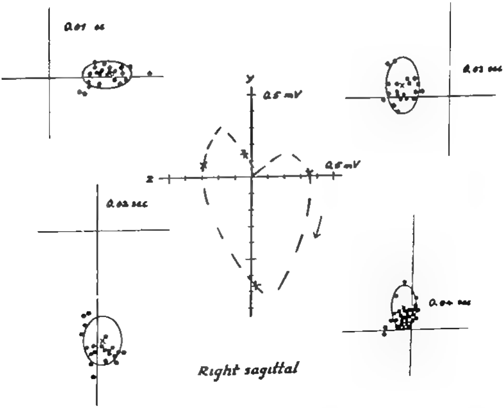
Frontal				Right sagittal				Horizontal			
X	= −0.186	Y	= −0.074	Z	= −0.297	Y	= −0.065	X	= −0.195	Z	= −0.297
S_x	= 0.116	S_y	= 0.200	S_z	= 0.100	S_y	= 0.168	S_x	= 0.127	S_z	= 0.113
S(x)	= 0.019	S(y)	= 0.032	S(z)	= 0.016	S(y)	= 0.027	S(x)	= 0.021	S(z)	= 0.018
$S(S_x)$	= 0.013	$S(S_y)$	= 0.022	$S(S_z)$	= 0.011	$S(S_y)$	= 0.019	$S(S_x)$	= 0.015	$S(S_z)$	= 0.013

0.04 sec.

Frontal				Right sagittal				Horizontal			
X	= −0.012	Y	= −0.154	Z	= −0.051	Y	= −0.141	X	= 0.088	Z	= −0.042
S_x	= 0.063	S_y	= 0.135	S_z	= 0.070	S_y	= 0.135	S_x	= 0.061	S_z	= 0.063
S(x)	= 0.017	S(y)	= 0.021	S(z)	= 0.011	S(y)	= 0.021	S(x)	= 0.010	S(z)	= 0.013
$S(S_x)$	= 0.010	$S(S_y)$	= 0.015	$S(S_z)$	= 0.008	$S(S_y)$	= 0.015	$S(S_x)$	= 0.007	$S(S_z)$	= 0.009



Frontal



Right sagittal

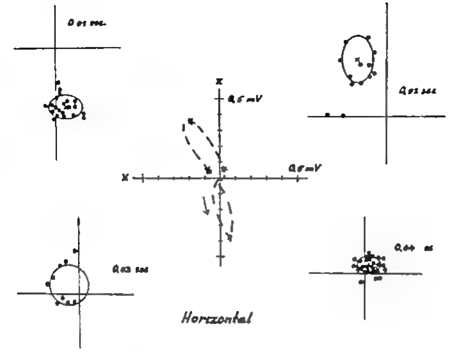


Fig. 20. Projections of the QRSaT instantaneous vectors in different planes and the typical loops for infants aged 21±1 days. For explanation, see Fig. 13. Numerical values: (mV)

Frontal

	0.01 sec.	0.02 sec.	0.03 sec.	0.04 sec.
x	0.077	−0.053	−0.187	0.022
S_x	0.085	0.187	0.105	0.063
$S(x)$	0.017	0.030	0.019	0.012
$S(S_x)$	0.012	0.014	0.014	0.008
y	−0.040	0.620	−0.059	−0.125
S_y	0.068	0.158	0.120	0.120
$S(y)$	0.012	0.047	0.022	0.022
$S(S_y)$	0.009	0.033	0.016	0.015

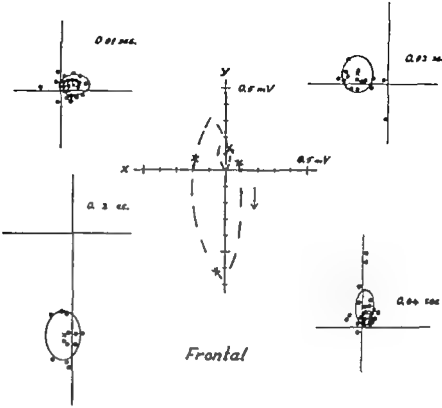
Right sagittal

	0.01 sec.	0.02 sec.	0.03 sec.	0.04 sec.
z	0.300	−0.033	−0.230	−0.042
S_z	0.090	0.137	0.130	0.046
$S(z)$	0.016	0.025	0.025	0.009
$S(S_z)$	0.012	0.018	0.018	0.006
y	−0.030	0.643	−0.090	−0.110
S_y	0.070	0.159	0.122	0.120
$S(y)$	0.013	0.029	0.024	0.024
$S(S_y)$	0.009	0.021	0.017	0.017

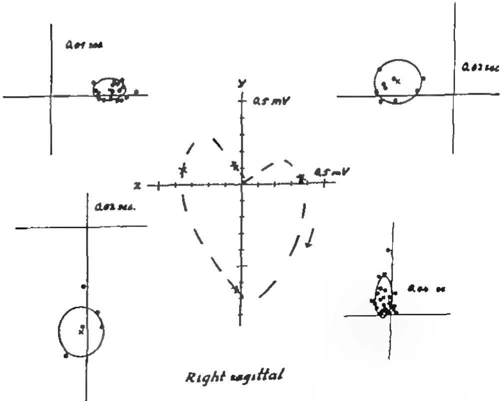
Horizontal

	0.01 sec.	0.02 sec.	0.03 sec.	0.04 sec.
x	0.089	−0.072	−0.137	0.028
S_x	0.111	0.131	0.096	0.072
$S(x)$	0.021	0.024	0.018	0.013
$S(S_x)$	0.015	0.017	0.013	0.009
z	0.374	−0.053	−0.337	−0.061
S_z	0.077	0.130	0.142	0.053
$S(z)$	0.015	0.024	0.026	0.010
$S(S_z)$	0.018	0.017	0.018	0.007

3



Frontal



Right sagittal

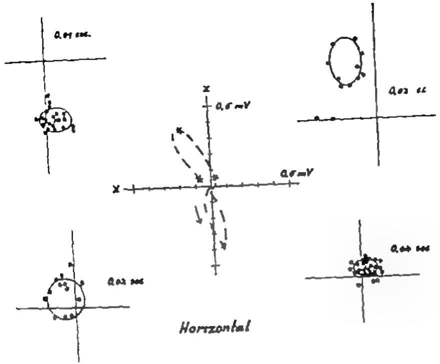


Fig. 20 Projections of the QRSaT instantaneous vectors in different planes and the typical loops for [illegible] aged 21±1 days. For explanation, see Fig. 12. Numerical values: (mV)

Frontal

Time	X	S_x	S(X)	$S(S_x)$	Y	S_y	S(Y)	$S(S_y)$
0.01 sec.	0.077	0.026	0.017	0.012	−0.040	0.068	0.012	0.009
0.02 sec.	−0.053	0.117	0.029	0.014	0.029	0.158	0.047	0.033
0.03 sec.	−0.187	0.105	0.019	0.014	−0.050	0.120	0.022	0.016
0.04 sec.	0.022	0.063	0.012	0.008	−0.125	0.120	0.022	0.015

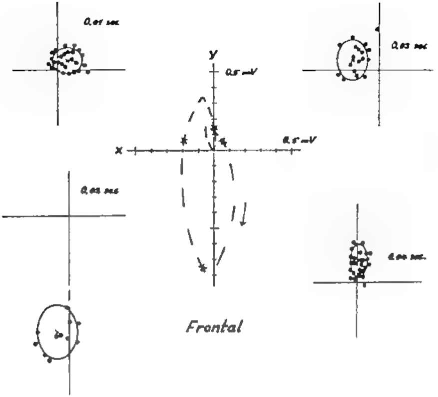
Right sagittal

Time	Z	S_z	S(Z)	$S(S_z)$	Y	S_y	S(Y)	$S(S_y)$
0.01 sec.	0.260	0.090	0.018	0.012	−0.030	0.070	0.013	0.008
0.02 sec.	−0.038	0.137	0.035	0.018	0.043	0.159	0.029	0.021
0.03 sec.	−0.350	0.130	0.025	0.018	−0.090	0.132	0.024	0.017
0.04 sec.	−0.042	0.046	0.009	0.008	−0.119	0.130	0.024	0.017

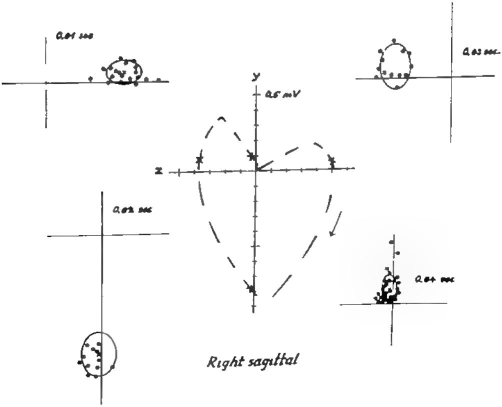
Horizontal

Time	X	S_x	S(X)	$S(S_x)$	Z	S_z	S(Z)	$S(S_z)$
0.01 sec.	0.069	0.111	0.021	0.013	0.374	0.077	0.015	0.010
0.02 sec.	−0.072	0.121	0.024	0.017	−0.053	0.130	0.024	0.017
0.03 sec.	−0.187	0.093	0.018	0.013	−0.357	0.142	0.026	0.018
0.04 sec.	0.028	0.072	0.018	0.008	−0.061	0.053	0.010	0.007

3



Frontal



Right sagittal

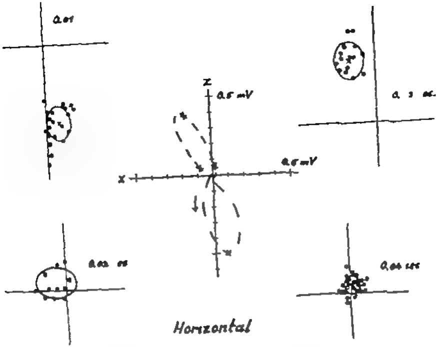
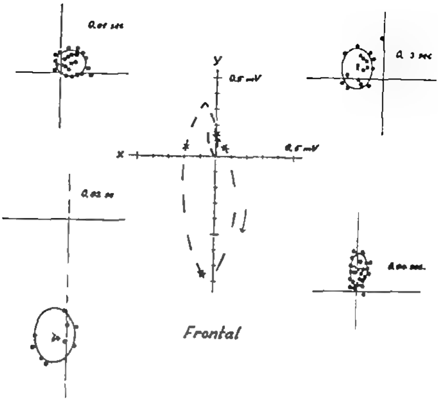
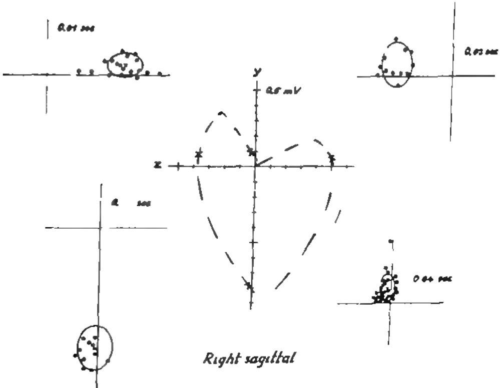


Fig. 21 Projections of the QRS&T instantaneous vectors in different planes and the typical loops for infants aged 28±1 days. For explanation, see Fig. 12. Numerical values: (mV)

	Frontal				Right sagittal				Horizontal			
0.01 sec.												
	x	0.063	y	−0.060	z	0.500	y	−0.067	x	0.073	z	0.503
	S_x	0.006	S_y	0.061	S_z	0.117	S_y	0.077	S_x	0.062	S_z	0.120
	$S(x)$	0.016	$S(y)$	0.015	$S(z)$	0.021	$S(y)$	0.014	$S(x)$	0.015	$S(z)$	0.022
	$S(S_x)$	0.012	$S(S_y)$	0.011	$S(S_z)$	0.015	$S(S_y)$	0.016	$S(S_x)$	0.010	$S(S_z)$	0.015
0.02 sec.												
	x	−0.070	y	0.767	z	−0.017	y	0.780	x	−0.080	z	−0.037
	S_x	0.133	S_y	0.172	S_z	0.118	S_y	0.142	S_x	0.124	S_z	0.113
	$S(x)$	0.025	$S(y)$	0.032	$S(z)$	0.023	$S(y)$	0.028	$S(x)$	0.025	$S(z)$	0.021
	$S(S_x)$	0.018	$S(S_y)$	0.023	$S(S_z)$	0.018	$S(S_y)$	0.018	$S(S_x)$	0.017	$S(S_z)$	0.015
0.03 sec.												
	x	−0.180	y	−0.063	z	−0.370	y	−0.070	x	−0.167	z	−0.384
	S_x	0.039	S_y	0.133	S_z	0.100	S_y	[illegible]	S_x	0.094	S_z	0.124
	$S(x)$	0.018	$S(y)$	0.025	$S(z)$	0.018	$S(y)$	0.027	$S(x)$	0.017	$S(z)$	0.023
	$S(S_x)$	0.013	$S(S_y)$	0.017	$S(S_z)$	0.013	$S(S_y)$	0.019	$S(S_x)$	0.012	$S(S_z)$	0.016
0.04 sec.												
	x	0.008	y	−0.145	z	−0.036	y	−0.110	x	0.020	z	−0.053
	S_x	0.053	S_y	0.036	S_z	0.053	S_y	0.101	S_x	0.054	S_z	0.060
	$S(x)$	0.010	$S(y)$	0.018	$S(z)$	0.010	$S(y)$	0.018	$S(x)$	0.010	$S(z)$	0.011
	$S(S_x)$	0.007	$S(S_y)$	0.013	$S(S_z)$	0.007	$S(S_y)$	0.013	$S(S_x)$	0.007	$S(S_z)$	0.008



Frontal



Right sagittal

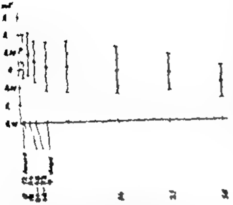


Fig. 22. Transverse components of the QRSsE 0.005 second instantaneous vectors in different age groups. Full-term and premature infants are included. The standard deviation on both sides of the mean is indicated.

great dispersion in the 0.02 and 0.03 second instantaneous vectors. This dispersion reveals, e.g., that the direction of inscription of the loop in the horizontal projection may be either clockwise or counter-clockwise in all the age groups, although the counter clockwise direction is rare in the youngest groups. The directions of inscription are listed in Table 6. Both directions, clockwise and counter clockwise as well as the figure-of eight, are seen in the horizontal projection in all age groups.

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Prematures and full-term newborn show the same *differences* that are seen more distinctly in the half area vectors, principally the slightly more anterior location of the 0.03 second vectors at the age of 1—4 days. The basic type of the loops, however is the same in both.

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0—12 hours	Clockwise							34	33	18						
	Figure-of-eight								1	10						
	Counter-clockw									6						
12—24 hours	Clockwise							28	30	16						
	Figure-of-eight							2		8						
	Counter-clockw									6						
24—48 hours	Clockwise	12	8	11	12	11	8	24	29	24	9	8	7	8	10	8
	Figure-of-eight	2	3	2	1	2	4	7	2	8		1	3	2		2
	Counter-clockw	1	5	2	1	2	3	1	1	2	1	1				
48—72 hours	Clockwise							29	35	15						
	Figure-of-eight							6		14						
	Counter-clockw									6						
3—4 days	Clockwise	12	10	10	13	17	8	47	46	30	6	3	8	9	8	6
	Figure-of-eight	2	4	4	3		3	7	7	20	4	5	1	1	2	3
	Counter-clockw	1	1	1	1		6	1	2	5		2	1			1
7±1 days	Clockwise	18	12	13	18	14	10	70	64	40	6	4	2	11	10	8
	Figure-of-eight	2	6	6	1	6	4	2	10	27	2	4	6	2	3	3
	Counter-clockw	2	4	3	1		6	2		7	2	2	2	2	2	4
14±1 days	Clockwise	18	13	12	20	20	8	37	35	15						
	Figure-of-eight	1	5	4			7	3	3	20						
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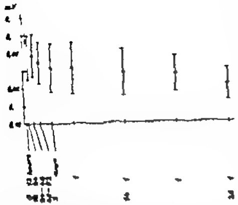

Fig. 22. Transverse components of the QRS and 0.005 second instantaneous vectors in different age groups. Full-term and premature infants are included. The standard deviation on both sides of the mean is indicated.

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	Figure-of-eight	2	2	2	1	2	4	7	2	6		1	3	2		2
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	Counter-clockw	1	1	1	1		6	1	2	5		2	1			1
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14±1 days	Clockwise	18	[illegible]	[illegible]	20	20	8	37	35	15						
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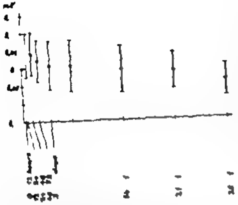

Fig. 22. Transverse components of the QRS-T 0.005 second instantaneous vectors in different age groups. Full term and premature infants are included. The standard deviation on both sides of the mean is indicated.

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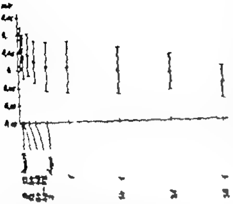

Fig. 22. Transverse components of the QRSaE 0.005 second instantaneous vectors in different age groups. Full-term and premature infants are included. The standard deviation on both sides of the mean is indicated.

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ber of degrees of freedom was n 1. Significance was denoted in the same way as elsewhere in this study (see p 41)

Grishman s cube system

Table 5 (page 33) shows the number and distribution into age groups of the recordings by this method. They were not performed on all the age groups because the primary object was to study the value of the system for the newborn.

For the same reason, only the QRSsÊ loop was examined. The QRSsÊ half area vectors and the maximal x, y and z components of the loops give the best idea of the differences from Frank s system. They are shown in Figs. 23 and 27 The most important differences from recordings made by Frank s system were

1. The spatial loops are smaller This is seen most distinctly in the frontal projection. The maximal x and y components are significantly smaller than in Frank s system.

2. The anterior potentials are markedly accentuated compared with other potentials. Some very weak posterior potentials are encountered, none at all in most recordings. There is a very highly significant difference between the cube system and Frank s in the antero-posterior ratio of the loop area in all the age groups. The difference between the sagittal components of the spatial half area vectors is also very highly significant. The same divergence between the cube system and Frank s system was noted by Massie and Walsh [146] and the preponderance of the right heart in the cube system compared with the other systems was observed by Rosen and Gardberg [188] and by Kimura and Toshima [117]

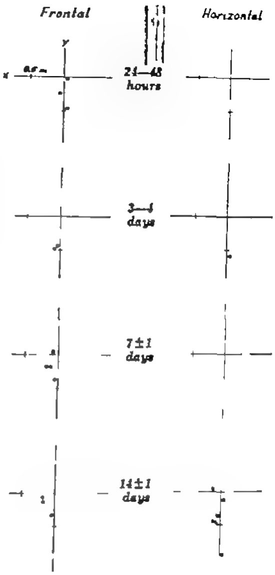

Fig. 23. Frontal and horizontal projections of the QRSsÊ half area vectors in recordings made by the cube system.

The dispersion in the recordings by the cube system was a little greater than in those by Frank s system.

There were no marked differences from Frank s system in the directions of inscription (Table 6)

There is no appreciable difference in practicalness between the two methods. The cube system is a little quicker because of its simplicity and the electrodes do not have to be posi tioned so accurately because not one is as close to the heart as the C electrode in Frank s system.

As far as interpretation is concerned, there is the disadvantage that the frontal projection is very small compared with the other systems. Frontal projection, however is often examined first as it is coordinated with the so-called standard leads of ordinary Ecg. Scalar Ecg taken by the same system also displays low amplitudes.

Wilson s tetrahedron system

Again, only the QRSaÊ loop was considered. The half area vectors are shown in Fig. 24 and the maximal x,y and z components in Fig. 27 Comparison with Frank s system showed the following differences:

1. The vertical component is heavily accentuated in the tetrahedron recordings. The spatial half area vectors are therefore located more inferiorly than in the recordings made by Frank s system, and the difference is significant in all the age groups, as it is between the maximal vertical components. This difference is due to the coefficients of the tetrahedron system. The coefficient of the vertical component is obviously too great. Frank also suggested this [61]

2. The loop is located significantly more anteriorly than in Frank s system but not as anteriorly as in the recordings made by the cube system.

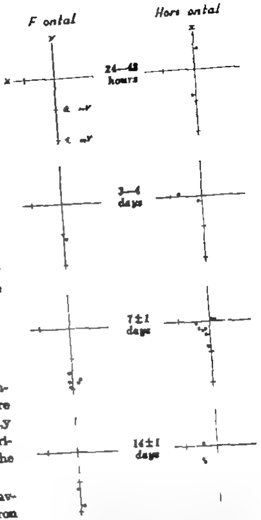

Fig. 24. Frontal and horizontal projections of the QRSaÊ half area vectors in recordings made by the tetrahedron system.

The dispersion was slightly greater with the tetrahedron than with Frank s system. There were no apprec iable differences in the directions of inscription (Table 6)

The tetrahedron system is the easiest of the systems used as regards

practicalness. The attachment of the electrodes to the limbs is easy and there are no difficulties of localisation. The dorsal electrode is the only one on the trunk. If an ordinary Ecg is made at the same time the same limb electrodes can be used The use of standardisation coefficients causes slight additional inconvenience since they must be adjusted separately for the different components. If the coeff icients were altered a little the tet rahedron system would compare better with the other systems for use in newborn and obviously also in larger children and adults.

Helm s system

The small number of recordings made by Helm s system gave the impression that it is not particularly suitable for use on the newborn. The half area vectors of the QRSaÊ loops are shown in Fig. 25, and the maximal x, y and z components in Fig. 27 Compared with the systems described above the following differ ences were noted

1. Helm s system greatly exagger ates the transverse potentials and the loops are therefore extremely wide in the frontal and horizontal projections. The difference from all the other systems used was very highly significant in this respect.

2 Some increase of the sagittal component compared with Frank s system was seen. It does not appear in the half area vectors, but the dif ference between the maximal sagittal components is highly significant (Fig. 27)

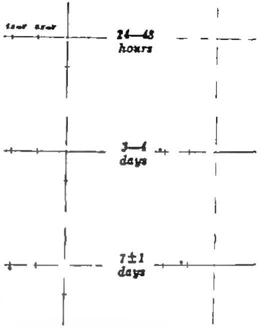

Fig. 25. Frontal and horizontal projections of the QRSaÊ half area vectors in recordings made by Helm s system.

The dispersion of the QRS half area vectors in the frontal and horizontal projections was greater than in the other systems, chiefly because of the accentuation of the transverse component, while the other components were roughly identical. This is why the dispersion of the instantaneous vectors is also unusually great. The lead vectors of the different components are obviously not of the same magnitude in the newborn with Helm s system. It is possible that the value of the method for use in the newborn could be improved by organising suitable resistances.

There were no appreciable differ ences from the other systems in the directions of inscription of the loops.

From the practical point of view too, Helm's system is not very suitable for studying newborn infants because its large sponge electrodes must be very accurately related to the size of the subject. This problem can be solved by having a series of suitable-sized electrodes for all newborn. The application of the electrodes takes a little more time than in Frank's system.

McFee's and Parungao's system

The half area vectors of the records made by McFee's and Parungao's system are presented in Fig. 28 and the maximal x, y and z components in Fig. 27. The half area vectors do not differ essentially from those of Frank's system. But there is a difference in the maximal sagittal component which is very highly significantly greater in McFee's and Parungao's system. However as the part of the loop located anteriorly is roughly as large as that located posteriorly in these age groups with both methods, the difference does not emerge in the half area vectors.

The dispersion with McFee's and Parungao's system was about the same as with Frank's system.

There were no appreciable differences from the other systems in the directions of inscription.

In the practical sense, the system of McFee and Parungao is not as good as Frank's because it requires more electrodes. The distances between the precordial electrodes and those on the left flank must be very

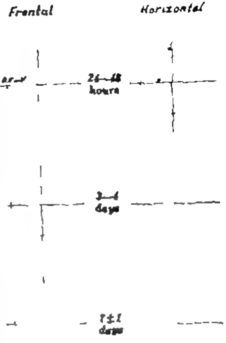

Fig. 28. Frontal and horizontal projections of the QRSaT half area vectors in recordings made by McFee's and Parungao's system.

carefully related to the size of the subject. If the infant is restless it is much more difficult to keep the electrodes in position.

Fig. 29 which shows recordings for a week-old full-term infant by all five systems, gives a good idea of the differences between the results of the systems used in this work. They were all made during the same day about midway between two meals, the first time by the cube and tetrahedron systems and the second time according to Frank, Helm, and McFee and Parungao.

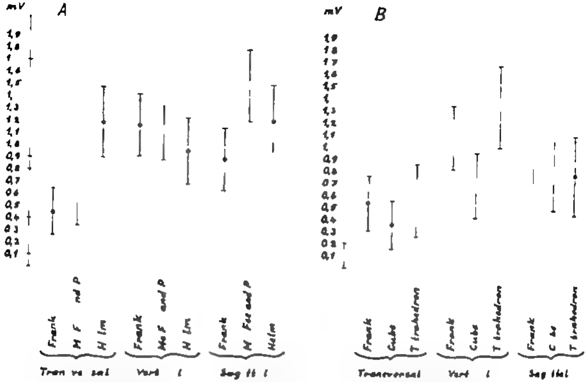

Fig. 27 The maximal components, parallel to the axes, of the QRSaE loops in recordings by different systems. The standard deviation on both sides of the mean is indicated. All the recordings in Fig. A were from the same infants, respectively and the same applies to Fig. B.

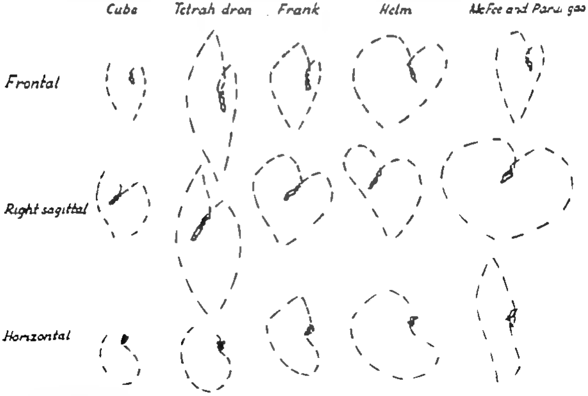

Fig. 28. Recordings from a week-old full term boy by all five systems. The typical differences between the systems are very distinct.

DISCUSSION

Since electrocardiography of the neonatal period has already been studied fairly extensively it is interesting to see whether the results of the present work really do provide new information concerning the electrical activity of the healthy heart in the neonatal period, elicited by vectorcardiography. If it does, the next problem is how far the findings are related to practical diagnostics. The latter aspect requires new studies using the same methods for both recording and analysis.

The findings selected for more detailed analysis here are such as cannot be obtained from scalar electrocardiograms. Everything that can be stated concerning them can therefore be said to add to our knowledge derived from ordinary electrocardiography. But, of course, much of the data is associated in some way with the findings given by electrocardiography.

QRSaE half area vectors are quantities characteristic of vectorcardiography. Although they have been compared with the mean vectors obtainable from scalar electrocardiogram [173] there is a very essential difference between them. Unlike all the quantities constructed from the surface areas of the waves of scalar Ecg, half area vectors are not a quantity integrated with time. Pipberger claimed that correct determination of the spatial half area vector and its projections takes one fairly close to a mean vector constructed from scalar Ecg [173] but this is valid only for normal recordings. For instance, terminal delay caused by bundle branch block does not change the location of the half area vector but affects essentially the mean vectors constructed from scalar Ecg. In contrast, the increase of terminal potentials to the right and upwards which occurs in e.g. hypertrophy of the right heart does not cause a major change in the mean vector constructed from scalar Ecg, unless accompanied by delay but does affect the half area vector very considerably.

The half area vectors determined in this study give an idea of the mutual relationship of the potentials of the different halves of the heart in the neonatal period and of the changes that occur in it during this period. It has been seen in many different connections that this relationship is revealed better by Vcg than by ordinary Ecg (see pp. 30—31). As was to be expected, the half area vectors are furthest to the right in the youngest age groups and this preponderance of the right heart decreases slightly already in the neonatal period. The difference between prematures and full-term newborn in this respect has

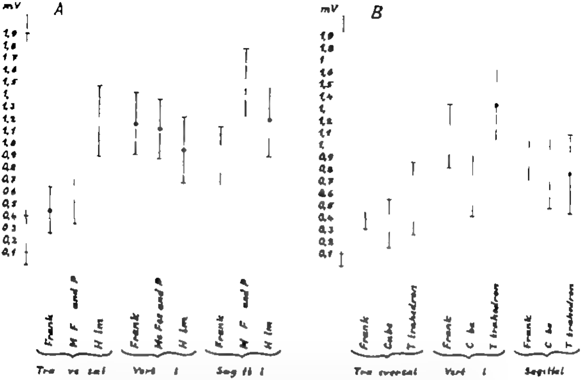

Fig. 27 The maximal components, parallel to the axes, of the QRSaß loops in recordings by different systems. The standard deviation on both sides of the mean is indicated. All the recordings in Fig. A were from the same infants, respectively and the same applies to Fig. B.

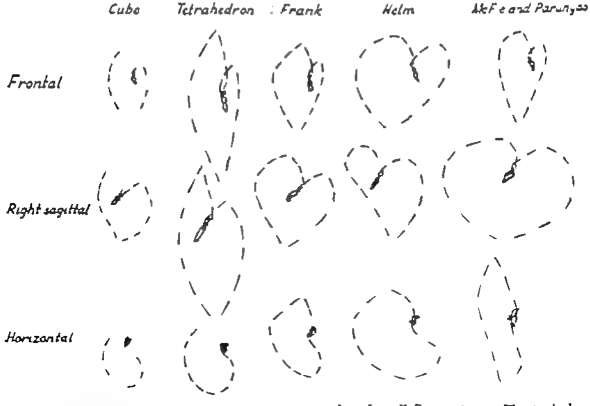

Fig. 28. Recordings from a week-old full term boy by all five systems. The typical differences between the systems are very distinct.

study or by a spatial rotator. However as we learn with practice to estimate the polar vector approximately from the loop projections, it can be employed in direct diagnosis once the normal value and dispersion for the age group in question is known.

Since the tortuosity of the QRSaE loop is great in the neonatal period, determination of the polar vector must always be slightly inaccurate. It is therefore possible that, in addition to the changes observed in elevation, minor changes may occur during the neonatal period also in the azimuth of the polar vector although the changes which occur in, say, the half area vectors need not necessarily be reflected in the polar vectors. The *present study gives the impression that the polar vector does not reflect quite so sensitively as the half area vector the small changes that occur in the relative strength of the different halves of the heart. On the other hand it is possible that also in the newborn, values outside the normal range indicate with all the more likelihood a pathologic cardiac finding.*

As far as the *QRS-T angle* is concerned, the importance of *spatial* determination must be emphasized. QRS-T angles have often been determined on different planes, but this can hardly be considered important. If the vectors that form the QRS-T angle deviate considerably from the plane in which their projections are examined, the size of the angle changes so much that every angle from 0 to 180 degrees may occur in the projection. Therefore, only the spatial QRS-T angles are presented in this study. Although they cannot be seen direct from the Vcg recordings, they can with a little practice be estimated roughly from the plane projections. Accurate determination can be performed rapidly by revolution and with a sphere.

The conclusion arrived at in this study is that the spatial QRS-T angle is not greater in the newborn than during later life. The values obtained for the different age groups are even a little smaller than the normal values recorded for adults [13]. Higher values have been reported for the newborn, according to Fowler 71 degrees, standard deviation 21 degrees [60]. Rothfeld *et al.* obtained considerably smaller values for QRS-T angles of the newborn in plane projections [189]. As the angles were fairly small on all planes, under 40 degrees in the majority of the cases, even the spatial QRS-T angles in their material could surely not have been very great.

There is in fact no reason why the spatial QRS-T angle of the newborn should be greater than it is later in life. When the preponderance of the right heart is physiologic in the newborn, there is no accompanying decrease in the concordance of QRS and T. *One criterion for distinguishing between pathologic and physiologic preponderance of the right heart may perhaps be the size of the spatial QRS-T angle in addition to the direction of inscription of the horizontal projection of the QRSaE loop* (see p. 30).

been established earlier by both ordinary Ecg [190 192, 224] and Vcg [139] The preponderance of the right heart is not as pronounced in prematures as it is in full-term newborn. According to the present study the half area vectors of premature and full term newborn in the frontal projection are approximately parallel from the age of two weeks. *The slighter preponderance of the right heart seen in prematures in the first 1—2 weeks of life* indicated by the conventional thorax leads as well, *is understandable because the relative strength of the different halves of the premature s heart in the first 1—2 weeks of life evidently corresponds still to the situation during the late fetal period* (see p 19)

More difficult to explain, on the other hand is the location of the half area vectors in the anteroposterior direction and the differences in this respect between prematures and full term newborn observed in this study Full term newborn reveal a shift in the anterior direction at the age of about one to two weeks, with Frank s method of recording, whereas the vectors of prematures are originally located more anteriorly — the difference is significant at the age of 1—7 days — and thus no notable changes occur in the neonatal period. The slight difference in the anatomic position of the heart between prematures and full term newborn is probably of significance in this respect.

The vectorcardiographic method is not as important for the *TsÊ half area vector* Owing to the small size of the TsÊ loop and its usually fairly narrow oval shape in the newborn, its half area vector is in practice very close to the maximal vector and mean vector The planimetrically determined half area vector is of importance here only when the TsÊ loop is broader than usual and thus larger in area or very irregular in shape.

The behaviour of T wave in the neonatal period has been studied extensively from scalar Ecg. Hait and Gasul [84] made a very detailed study of it from the very first moments of the infant s life albeit on a fairly small material. They called attention especially to spatial orientation. Although the results of the present study differ from theirs in that the TsÊ loops here are localised more inferiorly and posteriorly the difference is not of great importance in point of principle However it is not easy to obtain for the determination of the QRS-T angle a sufficiently accurate spatial orientation of the TsÊ loop from an ordinary Ecg. The value of the vectorcardiographic method is thus obvious here too.

The *QRSsÊ polar vector* is a typical vectorcardiographic quantity which cannot be constructed from an ordinary Ecg. Its diagnostic importance was stressed by Burger and Vaane [32] and Pipberger [175] It gives an idea of the location of the QRS plane and of the area of the spatial QRSsÊ loop. The polar vector is not so easy to establish from the projections of the QRSsÊ loop as the spatial half area vector it must be determined by revolution, as in the present

presented only in an orientating sense to facilitate the recognition of definitely normal recordings at first glance. There are great differences among normal recordings. The same components are usually not exactly of the same length in different projections. This is because every projection is recorded separately i.e. during a different contraction of the heart. If the recording system were complete and the electrical activity of the heart identical during the different contractions, the same component of the same magnitude would always be obtained independently of the projection. It is of course possible to make them all equal in size by recording all the projections simultaneously [79] or by measuring each component from only one projection and giving the corresponding component of the other projections similar values, as is sometimes done. The result, however does not then correspond to the true finding. The differences in the same component in different projections give some idea of the accuracy of the recording method, and presenting of the dispersion separately on all planes provides information on the variation of the findings on each plane separately.

The dispersion of the groups of spots, especially in the 0.02 and 0.03 second instantaneous vectors, shows that the loop configuration may change considerably. Rautaharju therefore called in question the significance of vector loop cardiography as a whole [160]. In certain cases, however the loop configuration also displays features which are highly diagnostic.

Paul *et al.* constructed typical loops from extreme vectors [163] but this method is somewhat incorrect for the reason mentioned above (p. 78). The results obtained by Paul *et al.* in their lowest age groups concur fairly well, nevertheless, with the results arrived at in the present study.

Taking the present results as a whole, it can be seen that the normal values for the neonatal period may be considered to be diagnostically significant values. Comparison with some other results obtained for the newborn shows that the dispersions are smaller in many respects in the present investigation. Since a fairly comprehensive material was studied by Frank's system, the statistical weight of the observations may be regarded as sufficient for diagnostic use. Technical experience in the performance of recordings and analysis of the results in studies of the newborn should be stressed.

Several lead systems can be used for vectorcardiographic study of the newborn. From experience in the present study Frank's system was found to be fairly serviceable. Owing to the special character of the subjects, it is hardly possible to adopt in clinical use methods that require very many electrodes. On the other hand, some factors that cause errors are especially strong in the newborn, e.g. specific anatomic characteristics, greater skin resistance restlessness, etc. Hence

The spatial QRS-T angle has a fairly considerable general importance in vectorcardiographic diagnosis. It is clear that the relations between the depolarisation and repolarisation of the ventricles of the heart are of great significance The ventricular gradient indicates the same relation. It is true that the ventricular gradient determined in the frontal plane the classical way is inaccurate and even during great changes in the T wave can remain within the normal range [181] The spatial ventricular gradient is a much better criterion [179] But if it is determined from conventional Ecg leads the inaccuracy is still considerable. *An accurately determined spatial QRS T angle using a corrected lead system for the Vcg recording obviously gives the best possible picture of the relationship between the depolarisation and repolarisation of the heart muscle*

QRSsÊ instantaneous vectors are very difficult to determine with absolute accuracy but reasonable accuracy can be achieved if the loop is traced as a broken line in the oscilloscope and the distance between the breaks in the line is fixed, e.g. 1/400 second. (The tecnique is described on p. 40) These instantaneous vectors are probably of considerable diagnostic importance. They can be used for temporal analysis of a certain part of the loop and for comparison of the differences in it between different subjects. Most other comparable quantities illustrate the loop in its entirety Another alternative is to compare so-called extreme vectors, but this method cannot be deemed reliable since an extreme vector of the same direction may be a vector of a completely different phase The extreme superior vector of the newborn may be e.g. an initial 0 005 second instantaneous vector or more often, a 0 035 second instantaneous vector and the extreme left vector may be similarly e.g. a 0 01 second or 0 04 second instantaneous vector etc. Their comparison thus cannot yield reliable results. The disadvantage of comparing instantaneous vectors, again, is that the vectors at the terminal part of the loop, such as the 0 04 second instantaneous vector in the newborn, are not associated in all subjects with the same electrical phase of the heart because the duration of the QRSsÊ loop varies. In most newborn this vector is associated with the extreme terminal phase of ventricular depolarisation. When, on the other hand the duration of ventricular depolarisation is as much as 0 05 or even 0 06 seconds, the 0 04 second instantaneous vector is then not associated with the terminal phase of depolarisation and, thus, is not comparable with the former However the majority of the newborn belong to the first mentioned group and the cases are comparable. Figs. 13—21 show that some of the 0 04 second instantaneous vectors are situated much more superiorly These are the instantaneous vectors of just those infants with a considerably longer than average duration of ventricular depolarisation.

The average types of the plane projections of the QRSsÊ loops are

SUMMARY

The purpose of the present study was to examine the value of the vectorcardiographic technique in the neonatal period, the technical requirements involved and the normal findings for newborn infants of different ages.

The material consisted of 250 newborn infants of whom 90 were premature. 360 Vcg recordings were performed on them by Frank's lead system. In addition, a smaller number of recordings were made by four other much used systems: Grishman's cube (72 recordings) Wilson's tetrahedron (72 recordings) Helm's (30 recordings) and McFee's and Parungao's (25 recordings).

In order to obtain normal values for newborn of different ages, recordings were performed for 9 age groups: 0—12 hours, 12—24 hours, 24—48 hours, 48—72 hours, 3—4 days, 7 ± 1 days, 14 ± 1 days, 21 ± 1 days, and 28 ± 1 days.

Special features of vectorcardiographic study of the newborn relating to the performance of the recordings and to analysis of the results are discussed.

The most important findings were

1. The vectorcardiographic technique lends itself well to use on the newborn. The dispersion of the results is generally no greater than later in life.

2. Frank's proved to be the most suitable of the lead systems used here for study of the newborn as regards practical clinical use and accuracy and reliability of the results.

3. The QRSsÊ half area vectors deviated to the right in the newborn in the same way *as the electrical axis* constructed from ordinary Ecg. In full-term newborn there was a gradual shift to the left and anteriorly during the neonatal period, after the first 1—2 days (Figs. 10—11).

4. The TsÊ half area vectors were mostly located posteriorly and inferiorly and gradually turned slightly to the left during the neonatal period (Fig. 12). An exception was the first day of the infant's life, most of the vectors being then anterior in direction.

5. The QRSsÊ polar vectors were directed to the left, slightly posteriorly and inferiorly. Azimuth averaged -24.7— 33.2 degrees in the different age groups and the corresponding elevation was +10.0 — +4.4 degrees (Table 3).

6. The spatial QRS-T angle was of the same magnitude in the neonatal period as later in life and the same was true of its dispersion. The means for the different age groups ranged from 35.5 to 61.0 degrees (Table 5).

7. The QRSsÊ instantaneous vectors were determined at 0.005 0.01,

corrected systems should be employed for clinical studies, too Of the corrected systems, Frank's combines in the author's opinion sufficient accuracy and practicalness and can consequently be recommended for routine use in the newborn. The other systems on the whole gave results that were so divergent that clinical recordings made by them could not be compared with the normal values obtained with Frank's system in this study

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9 The most important of the differences between the prematures and full term newborn were

a) The QRSsE half area vectors of the prematures during the first week of life were localised less to the right, and thus preponderance of the right heart was not as distinct as in full-term newborn (Figs. 7—8)

b) At under 2 weeks of age the QRSsE half area vectors of the prematures were localised distinctly more anteriorly than those of full-term *infants, except on the first day (Figs. 7—8)*

c) The same differences that were observed in the QRSsE half area vectors were naturally visible also in the QRSsE instantaneous vectors, but not quite so clearly

The conclusion reached is that the vectorcardiographic method can be recommended for clinical routine use in cardiac study of the newborn. For the recording procedure Frank s system is recommended, and for this the normal values obtained in this study can be used.

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Contents

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CHAPTER I

Introduction and aim of the investigation

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Surgical treatment of atrial septal defect of the secundum type was introduced during the 1950's by Bailey et al. (1952) Björk & Crafoord (1953) and Søndergaard (1954) among others, with different closed methods. The results of open heart surgery under hypothermia in atrial septal defect were described by Lewis and Taufic (1953) and Blount et al. (1954) and with the aid of extracorporeal circulation by Lillehei et al. (1955) among others. Since this period a large number of reports concerning investigations of atrial septal defects have been published.

Since several literature reviews on this subject ha e already been made, the reader is referred to the works of Reindell et al. (1962) Schrire and Vogelpoel (1964) Derra, Grosse-Brockhoff and Loogen (1965) and Zaver and Nadas (1965)

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The natural history and prognosis in atrial septal defect of the secundum type has been greatly discussed. Roesler (1934) Burrett and White (1945) and Bedford et al. (1957) found a mean life expectancy of 36—39 years. Campbell et al. (1957) and also Wood (1962) found, however that the prognosis in uncomplicated atrial septal defect of the secundum type was relatively favourable up to the age of 40—50 years, and according to Wood the object is to prevent considerable morbidity between the ages of 50 and 60 and to prevent death between the ages of 60 and 70"

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Since the long term prognosis in atrial septal defect of the secundum type, although difficult to assess, is not entirely favourable, and since the operation mortality is low Derra et al. (1965) conclude that in general, operation is indicated if the left to-right shunt is 30 per cent or more of the pulmonary blood flow A predominant right to-left shunt due to raised pulmonary resistance should constitute a definite contraindication to operation, as also should therapy resistant myocardial insufficiency

The *operation mortality in different* series of cases is always difficult to evaluate and varies amongst other things according to the selection of cases for surgery In an analysis made by the Committee on Cardiovascular Surgery American College of Chest Physicians (1963) a mortality of 3 per cent was reported in 397 patients operated on with different closed methods, while 542 patients had undergone operation under hypothermia, with 3 per cent mortality and 1206 patients operated on under extracorporeal circulation showed a mortality of 4 per cent.

In a series of 206 "good risk" patients with uncomplicated secundum defects subjected to operation under hypothermia, Sellors (1961) reported a total mortality of 0.5 per cent, and approximately the same result was obtained by Derra et al. (1965) with only two deaths among 215 such patients. Derra states that the total operation mortality in atrial septal defect of the secundum type is now probably lower than 2 per cent in most thoracic surgical centres. In view of the gradual reduction of the operation mortality in open repair of atrial septal defects of the secundum type, it is sometimes considered that the diagnosis in itself constitutes an indication for operation (Zimmerman 1958 Mustard 1961 Gasul et al. 1961) but other authors (Taussig 1960 Gross 1962 Wood 1962) are of the opinion that with small defects, which are usually compatible with a normal life operation is not usually indicated.

Partly owing to variations in the selection of patients and the operation technique, the operation results in different series of cases, *often expressed as the* mortality rate and the number of residual shunts, are difficult to compare. In one of the first investigations made after closed heart operations in atrial septal defect Kirklin et al. (1956) found 6 residual shunts in 20 recatheterized patients, among 32 operated on by the Gross method At the same time "a mild drop in pulmonary artery pressure even when it has been within the range of normal prior to operation" was shown.

Sondergaard (1962) found a functionally closed defect in all except one of 66 recatheterized patients in his own operation series, although the defect was completely closed in only 54 patients. Carlgren (1961) found small residual shunts in 9 of a smaller series of 24 patients operated on by the same method

Residual left to-right shunts have also been demonstrated after open repair of atrial septal defects. These have usually been of a lower frequency but varying figures of up to 20 per cent are reported. Bedford et al. (1957) investigated 40 patients after operation under hypothermia, including 12 with cardiac cathe

terization. A residual shunt was shown in 5 patients. Winchell and Bashour (1958) compared the haemodynamic conditions at rest before and after operation under hypothermia in 20 patients with atrial septal defect of the secundum type, and found a residual left-to-right shunt in only 1 patient, who was found at operation to have an undiscovered anomalous pulmonary vein opening into the superior vena cava. In summary these authors state that "closure of the atrial septal defect brought about the changes that one would anticipate such as reduction of pulmonary blood flow and pulmonary artery pressure to normal if it was initially elevated".

Among 65 patients with atrial septal defects of the secundum type, catheterized after operation under hypothermia, Sellors (1961) found small residual shunts in 7 patients "operated on in the early days of open heart surgery".

A large series of followed up uncomplicated atrial septal defects of the secundum type is reported by Loogen and Toker (1961) who examined 100 patients 1—6 years after operation under hypothermia. Of these patients 43 were recatheterized 4—6 weeks after operation, and 7 (16 per cent) were then found to have a residual shunt. In the remaining cases changes of the physical, electrocardiographic and roentgenological findings indicated that the defect was closed.

In a series of 30 secundum defects examined by cardiac catheterization 1—4 years after operation under hypothermia, Reindell et al. (1962) gave a full report of the roentgenological findings before and after operation. A residual left-to-right shunt was noted in 2 patients of this series.

The subjective improvement, and alterations in the physical cardiac findings and electrocardiographic and roentgenological conditions after closure of atrial septal defects are, as a rule, described together with the catheterization results, and such reports have been made by Bedford et al. (1957), Loogen and Toker (1961), and Reindell et al. (1962) among others.

An analysis of postoperative changes has been made recently by Derra, Grosse-Brockhoff and Loogen (1965). The electrocardiographic findings before and after repair of atrial septal defect have been described especially by Davies et al. (1960) and Lee and Scherlis (1962); in these series, however, no catheterization data are given to show that the defect has been closed.

Up to the present no comprehensive study of a large series of patients following open repair of atrial septal defect appears to have been reported.

Aim of the investigation. The present investigation is based on 105 patients recatheterized 17.3 months, on the average, after open correction of an *atrial septal defect of the secundum type* (ASD sec), with or without partial anomalous venous return, and 2 patients with partially anomalous venous return but with no defect.

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3 The haemodynamic conditions in a number of these patients, during work after the operation, with conditions in normal persons.

4 The haemodynamic findings at rest and during work in a number of patients, both before and after the operation in greater detail and also to compare these results with conditions in normal persons.

Case material

Collection of the material was begun in 1958, when open repair under hypothermia was introduced as a routine operation method for atrial septal defect of the secundum type at the Department of Thoracic Surgery University Hospital, Uppsala. Up until June 1964 115 patients with this diagnosis had been operated on by V O Björk personally head of the department at that time. Of these, 107 patients were followed up and form the basis of this study Five patients were not available for follow up examination, and a further three patients had died.

The majority of these patients had been remitted to the Cardiac Division of the Medical or Paediatric Medical Clinic University Hospital, Uppsala, from different hospitals, with a preliminary diagnosis such as congenital heart disease or atrial septal defect" for investigation and decision as regards surgery The diagnosis was then established by means of a complete cardiological investigation. The indication for operation was left to-right shunt on the atrial level of at least 30 % of the pulmonary blood flow In no case was there a predominant right-to-left shunt on the atrial level, or any other contraindication for operation.

Mortality There was no primary operation mortality The total mortality hitherto has comprised 3 patients (2.6 %) One 33-year old woman died of a cerebral embolus 9 days after the operation. In one 42-year old woman a postoperative regularized fibrillation necessitated the continuation of anticoagulant therapy after her discharge from hospital This patient died at her local hospital 8 months after the operation, of a cerebro-vascular complication which was probably drug induced. The third patient, a 35-year old woman, died 3 years after the operation in cardiac failure. At the operation a left to-right 80 % shunt was found, and moderate pulmonary hypertension with a systolic pulmonary arterial pressure of 50 mm Hg. Roentgenologically this patient exhibited marked cardiac enlargement with a relative volume of 1420 ml/m² body surface area, expressing pronounced myocardial insufficiency Postoperatively there was no residual shunt, and there was some subjective functional improvement, but there was a manifest, therapy-resistant cardiac insufficiency with pronounced cardiac enlargement and a roentgenological volume of 1000 ml/m² body surface area.

Age and sex. The patients were divided into the following three age groups according to age at the time of operation.

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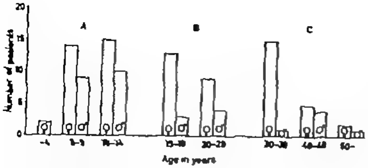


Fig 1 Distribution of patients at time of operation, by age and sex.

Age group B comprised a group of 29 young adults who were operated on at the ages of 15—29 years.

Age group C comprised a group of 28 older adults, who at the time of operation were 30 years old or older

The youngest patient was 3 years old at the time of operation, and the oldest 62 years.

The material consisted of 75 women and 32 men, the ratio of women to men being thus 2 3 1 The sex distribution varied somewhat in the different age groups. In age group A there were 31 girls and 19 boys (ratio 1 6 1) Age group B comprised 22 women and 7 men (ratio 3 1 1) and age group C 22 women and 6 men (ratio 3 7 1) The age and sex distributions at the time of operation can be seen in Fig 1

Operation methods Open repair of the atrial septal defect under hypothermia was performed in 94 of the 107 patients investigated. In 13 cases the operation was carried out with the aid of extracorporeal circulation In one 7 year old girl extracorporeal circulation was used because of uncertainty in the diagnosis ASD of primum type could not be excluded with certainty Two young adult patients in age group B, who had previously undergone surgery by the Sondergaard method, were re-operated on with the aid of extracorporeal circulation. Among the older adults of age group C, extracorporeal circulation was used in 3 patients in whom ASD of primum type could not be excluded with certainty and this method was also preferred in a further 7 patients with a large left to-right shunt. The surgical method for correction of ASD sec has been described in detail previously by V O Bjork et al. (1960) and for correction of anomalous venous return by V O Bjork et al. (1962)

Postoperative complications In 5 adult patients cerebral emboli occurred during the first few days postoperatively In 1 of these patients the outcome was fatal. The remaining 4 patients showed rapid clinical improvement, and on discharge from hospital there were no clinico-neurological abnormalities.

Fourteen patients, 12 of whom were older persons with a large left to-right shunt and cardiac enlargement, required postoperative respirator treatment for an average of 7 5 (1—26) days.

In one patient a cardiac rhythm disturbance (A V block III) occurred during the operation, and this necessitated continuous pacemaker treatment. In 10 adult patients local infection occurred in the thoracotomy wound, and in some cases this prolonged considerably the pe

riod of postoperative care. One child developed a bacterial hepatic venous thrombosis, and one adult patient bacterial pericarditis, but both recovered.

Period of postoperative care The duration of *hospitalisation* after the operation was, on the average, 21 (12—45) days for children, 36 (14—120) days for the younger adults and 40 (20—100) days for the older adults.

The *convalescence period* was also considerably shorter for the children, being 3.5 (2—12) weeks compared with 11.5 (12—36) weeks for the younger and 20.5 (12—60) weeks for the older adults.

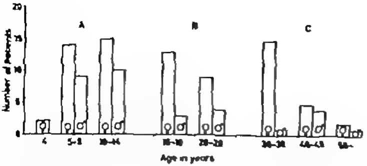
Observatio time The observation time between operation and follow-up examination was, on the average, 17.3 months, with some variation between nd within the different age groups. On the a erage the children were investigated 8 (5—33) months and the adults 25 (15—70) months after the operation. This difference is explained by the fact that the children were called for follow up as routine w thin 1 year after the operation, whereas the adult patients were called in especially for this investigation, the patients who were operated on earliest being followed up first.

I the following, the term postopera tiv refers to the time of the follow-up examination.

Type f d fect At operation 55 patients were found to ha e a central secundum defect. Twenty two patients had large low secundum defect, and in 12 of them this was of the inferior ena ca a defect type w th no posterio-caudal margin. Twenty-seven patients had a sinus enosus defect, which in 17 cases was combined with partial anomalous venous return. A further 3 patients had anomalous venous return, in one case combined with a large central defect and in two cases with no apparent defect. The frequency of partial anomalous venous return in the entire material was 18.7 %. In 15 patients with a sinus venosus defect, and in two cases with no visible defect there was right-sided anomalous venous return to the superior vena cava, in two cases to the right atrium and in one patient to both the right atrium and the inferior vena cava.

Other cardiac malformations. In 5 patients other complicating cardiac malformations were found. Three women had mild valvular pulmonary stenosis. In 2 of these cases double repair was carried out at the operation, whereby the atrial septal defect was first closed, and valvulotomy was then performed. From a haemodynamic aspect, however the atrial septal defect predominated over the pulmonary stenosis, and these patients were therefore included.

Two patients with mitral insufficiency a woman and a man both of age group C, had both had rheumatic car diac disease. The man underwent operation with the aid of extracorporeal circulation, at which a mitral annuloplasty was performed at the same time. In the woman there appeared to be no indication for treating the mitral insuf ficiency when the atrial septal defect was repaired. Myocarditis had occurred in 2 children. One of them, a 7-year old boy had had viral myocarditis (influenza type A) and also, two years later rheumatic myocarditis. The other child, a girl, had had probable viral myocarditis



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older age groups is probably not an excess mortality in the men, but could perhaps be that with symptoms of the type suffered by these patients, medical advice is more often sought by women than men (Campbell and Polani, 1962)

Distributions of defect types in operation series have been reported only seldom, but the distribution in the present material is in approximate agreement with the similarly classified series of Sellors (1961) and Arntzenius et al. (1963) The central or fossa ovalis defect constituted 60—80 % of all defects. The frequency of partial anomalous venous return was in the present series 18.7 % which is in agreement with the figures of 10—20 % reported by Derra et al. (1965)

The frequency of malformations of the mitral valve in patients with atrial septal defect varies in different series (Bedford et al. 1957 Derra et al. 1965) being partly dependent on the incidence of rheumatic fever among the population, and the age composition of the material. In Sweden the incidence of rheumatic fever has long been low (Hall 1961) which may explain the low frequency of rheumatic mitral valvular disease in this series.

in her infancy In neither of these cases were valvular changes observed on examination or operation. There were no patients with both atrial septal defect and mitral stenosis (Lutembacher's syndrome) in this series.

There were no patients with a history of endocarditis lenta in this series.

Discussion

The present material comprises a series of operation cases of atrial septal defects of the secundum type, where by chance there were no severe haemodynamic complications. It has been found that in cases where partial anomalous venous return is present in addition, this produces no change either in the clinical picture or the haemodynamic findings (Kjellberg et al. 1959) and patients with such a condition were therefore included in the ASD series.

It must be accepted that in a clinical investigation of this type there will be some degree of change in the material due to time-dependent factors such as body growth. Usually it is assumed that the haemodynamic conditions will not have returned to normal after repair of an atrial septal defect of the secundum type until about a year after the operation (Reindell et al. 1962) In most of the adult patients in the present series the postoperative observation period was considerably longer but in other cases the period was shorter Nevertheless certain results obtained at the follow up examination were used for comparisons, since the observation periods in the different age groups were considered sufficiently long

The total mortality during the period covered by the investigation was 2.6 %. When however the mortality was calculated on the basis of operative and postoperative death, i e. within 10 days after the operation (Nordlund 1966) it was only 0.9 %. The two deaths occurring 2 months and 3 years after the operation, respectively were late deaths (after 10 days) and should not be included in comparisons with other operation mortality figures. This operation mortality of 0 9 % is thus of the same order of size as has been reported by Sellors (1961) and Derra et al. (1965) among others.

In evaluations of the operation risk in uncomplicated atrial septal defect of the secundum type the most suitable age for operation has been discussed. In this series the age distribution at the time of operation was in agreement with that usually seen in ASD sec (Bedford 1961 Zellos 1964) Even if the operation risk increases with advancing age, a high age is not considered in itself to be a contraindication to operation (Ellis et al. 1960) however the optimal age for closure of an atrial septal defect of the secundum type is considered to be between 5 and 15 years (Mark 1963) In the present series this corresponds to the patients in age group A, and for these patients both the period of postoperative care and the convalescence period were considerably shorter than for the young and older adults.

The sex distribution in the whole material agreed with that usually reported in secundum defects (Derra et al. 1965 Himbert et al. 1965) The reason for the predominance of women over men in the

three heart cycles was used. With high QRS amplitudes the amplification was reduced so that one mV corresponded to 5 mm, compared with the usual 10 mm. The paper speed was 50 mm/sec. The mean QRS axis in the frontal plane was calculated in the usual way with values for axis deviation according to Goldman (1960)

For checking the rhythm postoperatively usually only standard and extremity leads could be used for the first 6—8 days because of the extent of the operation wound. At the exercise tests ECG was recorded in the recumbent position, after 8 minutes of passive standing, during exercise, in the sitting position and both immediately and 4 and 10 minutes after exercise in the recumbent position. During exercise a CH lead with the indifferent electrode on the forehead was used (Sjöstrand, 1951 Holmgren and Strandell, 1961)

Phonocardiogram (PCG) The calibrated phonocardiogram was recorded by means of the same four-channel ECG direct writing apparatus with a phonopreamplifier Usually filters with nominal frequencies of 25 c/s and 100 c/s, and an auditory amplification (Kjellberg et al. 1959) were used. The paper speed was 100 mm/sec. The recordings were made after normal expiration, over the second right, the second and third left and the fourth left intercostal spaces, and over the apex. Special respiratory phonocardiograms" for the evaluation of the second sound during ordinary inspiration and expiration were recorded. The time interval between the sound components was determined from the mean of at least 5 measurements, the interval being measured between the initial maximal amplitudes of the different components.

Basal metabolic rate The basal oxygen uptake was measured by means of double determinations of ten minutes duration each, using a Spirograf Krogh or "Spirograf IV" (Elema-Schönander Ltd., Stockholm)

Physical work capacity A work test with step-wise increases of the load (Sjöstrand, 1947 Wahlund, 1948) was carried out in the usual way on an electrically braked bicycle (Holmgren and Mattsson, 1954) The heart rate was determined after 2, 4 and 6 minutes, and the respiratory rate was counted after about 5 minutes at each load. The ECG was monitored continuously on the oscilloscope, and was recorded after 5 minutes at each load. For children under 12 years of age the first load was usually 100 kpm/min, for older children and women 200 kpm/min and for men 300 kpm/min. The test was discontinued when the pulse rate reached approximately 170 beats/min, or earlier in the event of objective or subjective signs of an abnormal reaction. The work capacity corresponding to a heart rate of 170 beats/min (PWC_{170}) was obtained by means of extrapolation or interpolation and was expressed as kpm/min per kg body weight. Work capacities of 600 kpm/min for women and 900 kpm/min for men were usually regarded as normal. The children were evaluated according to Sterky (1963)

Heart volume. The heart volume was determined with the patient in the sitting position according to the method of Jonsell (1939) and the relative heart

CHAPTER III

Methods

The mode of investigation was the same preoperatively as at the follow up examination. On both occasions the patient was hospitalized, the period of hospitalization being about 7 days for the preoperative examination and 3—4 days for the follow up

In all cases these investigations comprised a general clinical examination with full examination of the physical cardiac state electrocardiogram and phonocardiogram, chest roentgenogram and cardiac catheterization. On catheterization the pressure and flow were determined at rest and during exercise both pre and postoperatively in 18 patients, using the same work load on each occasion, and postoperatively alone in 51 patients.

General clinical examination Physical examination was performed personally by the author in all of the follow-up and also in most of the preoperative investigations, particularly in the children. The case history data concerning the symptoms and functional capacity were evaluated and used as a basis for division into function classes. For adults, function classes as suggested by the New York Heart Association (1964) were used and for children a modification of Davidsen s classification (1960) The general condition was assessed with especial regard to cardiac failure and complicating diseases, and to any further congenital malformations.

The physical cardiac state was evaluated with respect to palpatory precordial activity and auscultatory findings. The palpatory findings were assessed, and signs of increased right ventricular activity were noted. The intensity of the first sound, the degree and variability of splitting of the second sound and the amplitude of the pulmonary component were assessed. The distribution and site of the murmur were determined and the systolic murmurs graded according to Levine & Harvey (1959) at the position of their maxima. Routine blood and urinary analyses were carried out.

Electrocardiogram (ECG) In the great majority of cases the ECG was recorded with a four-channel direct writing apparatus (Mingograf 42 Elema Schönander Ltd., Stockholm) and in only a few patients before 1959 was the recording made on a three-channel apparatus (Triplex, Elema) Leads I II III aVR, aVL and aVF were used, and also in adults precordial leads V_1—V_7 and in children precordial leads V_1—V_8.

On evaluation of the QRS complex and the P and T waves, the amplitudes were measured from the isoelectrical line, i. e. a line drawn between two TP segments The mean value of at least

blood. The left-to-right shunt expressed in this way has been compared with the ratio of the pulmonary blood flow $\dot{Q}_p$ to the systemic flow $\dot{Q}_s$ (Table 2). On the basis of these considerations the following three "shunt groups" were used.

Shunt group 1. Left-to-right shunt of less than 50 % of the pulmonary blood flow corresponding to a $\dot{Q}_p : \dot{Q}_s$ ratio of less than 2 : 1.

Shunt group 2. Shunt of 50—65 % corresponding to a $\dot{Q}_p : \dot{Q}_s$ ratio equal to or more than 2 : 1 but less than 3 : 1.

Shunt group 3. Shunt of 66 % or more, corresponding to a $\dot{Q}_p : \dot{Q}_s$ ratio equal to or more than 3 : 1.

The pressure and ECG recordings were made on a direct-writing four-channel ECG apparatus (Mingograf 42). The mean pressure was obtained by electrical integration. Pressures were usually recorded continuously on withdrawal curves from the pulmonary capillary venous position to the superior vena cava for the evaluation of any valvular stenoses. In many cases the pressures in the left atrium and ventricle could be recorded preoperatively via the defect.

No complications occurred on right heart catheterization either preoperatively or at the follow-up examination, nor at the preoperative left heart catheterization performed in 47 patients.

For flow determination the catheter was placed in the pulmonary artery. The cardiac output was measured by the direct Fick method. Pressure recordings were made and blood samples taken during the 5th to 8th minutes at rest and 4th to 6th minutes during exercise. Expired air was collected for 10 minutes

Table 2. Size of left-to-right shunt expressed as per cent of pulmonary blood flow, compared with $\dot{Q}p:\dot{Q}s$ ratio.

Left-to-right shunt % of pulmonary blood flow	Pulmonary blood flow ($\dot{Q}p$) in relation to systemic flow ($\dot{Q}s$)
33	1.5:1
50	2 : 1
66	3 : 1
75	4 : 1
80	5 : 1
83	6 : 1
87	7 : 1
89	8 : 1

with the patient at rest, and for 3 minutes during exercise, between the 3rd and 6th minute of each load, with the Douglas bag technique. Gas analyses were performed according to the Haldane technique (Enghoff 1946). Normal values for oxygen consumption were obtained from current tables (Harris and Benedict, 1919; Nadas, 1963).

Oxygen saturation. In most cases, where repeated oxygen saturation determinations were made at short intervals, a Kipp haemoreflectometer (Kipp and Sons Company, Delft, the Netherlands) was usually used, according to the method originally described by Zijlstra (1953). This method was employed in comparisons of pre- and postoperative saturation values. For flow determinations the oxygen saturation was measured by spectrophotometry of haemolysed whole blood, as described by Holmgren and Pernow (1959). The haemoglobin concentration was determined spectrophotometrically as cyanmethaemoglobin.

TABLE 1 Heart size ml/m^2 BSA, according to X ray groups in children, women and men.

Heart size	Children	Women	Men	
Normal	<350	<450	<500	ml/m^2 BSA
Slight enlargement	>350—500	>450—600	>500—650	»
Moderate enlargement	>500—650	>600—750	>650—800	»
Pronounced enlargement	>650	>750	>800	»

volume is given in ml/m^2 body surface area. The group classification can be seen in Table 1

Lung function tests The lung volumes and ventilation capacity were determined with a "Spirokombi" (Kifa Ltd., Stockholm) The vital capacity (VC) forced expiratory volume in one second ($FEV_{1.0}$) and maximum voluntary ventilation with a fixed respiratory frequency of 40 (MVV_{40}) and with a free respiratory frequency (MVV_f) were measured. By FEV % is meant $FEV_{1.0}$ expressed as a percentage of VC or FVC (forced vital capacity) depending on which is the greater

Cardiac catheterization. Before the first catheterization the patient was well informed about the investigation there were no difficulties in obtaining the patient's cooperation for follow up catheterization after the operation. In the morning, approximately 1 hour before the catheterization the children were given a small dose of morphine (5—7 mg) subcutaneously and the adults were given a small oral dose of Pentymal (0 1 —0 2 g) The catheterization was performed with the patient in the recumbent position. A polyethylene catheter was introduced into the brachial artery by the usual percutaneous technique. The venous catheter was usually introduced via an exposed superficial cubital vein but in some cases, especially children, the saphenous vein was preferred. In most cases the defect was demonstrated preoperatively by means of the catheter In many cases, especially with catheterization via the superior vena cava, a good idea of the position of the defect in the septum could be obtained by manipulation of the catheter as has been described by Gotzsche (1962) Shunts were usually determined preoperatively from the oxygen saturation values with relatively rapid withdrawal from the pulmonary artery to the superior vena cava. An increase in oxygen saturation of 10 per cent in one set of samples between the superior vena cava and the pulmonary artery is regarded as evidence of a left to-right shunt (Nadas, 1963) It is routine at our Centre to express the size of the left to-right shunt as per cent of the pulmonary blood flow Q % LR, (Hamilton and Dow 1962) as follows

$$Q\,\%\,LR = \frac{C_{PA_{O_2}} - C_{\bar{v}_{O_2}}}{C_{PV_{O_2}} - C_{\bar{v}_{O_2}}}$$

$C_{PV_{O_2}}$ and $C_{PA_{O_2}}$ are the oxygen contents of pulmonary vein and pulmonary artery samples, respectively and $C_{\bar{v}_{O_2}}$ is the oxygen content of mixed venous

blood. The left-to-right shunt expressed in this way has been compared with the ratio of the pulmonary blood flow $\dot{Q}_p$, to the systemic flow $\dot{Q}_s$ (Table 2). On the basis of these considerations the following three shunt groups were used:

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Statistics. The arithmetical mean, standard deviation (SD) and standard error of the mean (SE) were calculated by the conventional methods. Student's t test was used to determine the significance of the differences in the various variables between preoperative and postoperative values. The studies of relations between the different variables were performed on the basis of the correlation coefficients where the significance was also determined by the t test (Snedecor 1956).

The significance levels applied were as follows

$0.05 \geq P > 0.01 = (*)$
$0.01 \geq P > 0.001 = (**)$
$0.001 \geq P = (***)$

These values correspond to the usual terms "probably significant", "significant" and "highly significant" respectively.

CHAPTER IV

Clinical findings before and after operation

Growth and physical development

The height and weight in relation to age were determined in 66 patients below 20 years of age (45 girls and 21 boys). There was some tendency to underweight, especially in the younger patients, but in only a few were the values found to be outside the normal (± 2 SD) range limits for Swedish children (Karlberg & Iggbom, 1959) as can be seen in Fig. 2. In some patients the weight was lower than the normal at the follow-up examination also, in spite of a normal weight increase.

Height in relation to age at operation. In 61 of the 66 patients the height in relation to age was within the normal range for healthy Swedish children. In 2 boys the height was below the lower range limit and in 2 other boys above the upper limit, but in all four boys the weight was normal. In one patient there were hereditary factors to explain her short stature (a Lapp girl).

Weight in relation to height at operation. Only in 5 patients, 4 girls and 1 boy was the weight found to be below the normal limit, but in all of these patients except one the height-age relationship was normal. The exception was a 14-year old boy who was unusually tall and gracile with a height of 20 cm above and a weight of 5 kg below the normal limits of variation. One girl had a pronounced weight excess.

Height in relation to age at follow-up examination. At the follow-up examination it was found that the height increase was normal, and agreed with the growth diagram. In 2 out of 3 patients whose preoperative height lay somewhat outside the normal limits of variation, the height increase was normal. The third, the gracile boy mentioned above, had increased in height by a further 13 cm to 203 cm in 18 months.

Weight in relation to height at follow-up examination. In 9 girls at the age of puberty the weight increase was rather more pronounced than the normal. In two of these the weight before the operation lay below the normal limit. In two patients the weight still lay below the normal limit in spite of a normal weight increase. One 18-year old girl who was considerably overweight preoperatively increased a further 20 kg. In the remaining patients the weight increase was normal. Preoperatively the weight in relation to height lay near the lower normal limits in patients up to 15 years of age but postoperatively there was a weight increase which meant that the deviation from the mean value diminished significantly (*).

In 41 patients of ages 20—67 years, the weight—height relationships showed no special tendencies either pre- or postoperatively.

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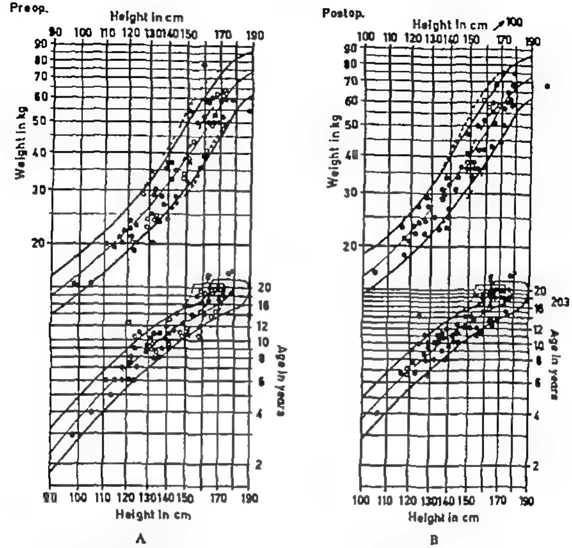


Fig 2 Physical development in 66 patients before (A) and after (B) operation. — The growth diagram gives the height in relation to age, and weight in relation to height, mean value ± SD in healthy Swedish children according to Karlberg and Igbom (1959)

Symptoms

The symptom pictures in the different age groups among a total of 44 patients with a history of functional reduction are shown in Table 3 The predominant symptoms at all ages were increased exhaustibility and breathlessness, these occurring as the only symptoms in 36 out of 38 patients in function class II two patients in age group B stated that they had no increase in exhaustibility despite their breathlessness. 9 patients also had palpitations, which in two of them were associated with precordial pain.

Only age group C included patients with pronounced subjective symptoms, 6 of them being assigned to function class III. These six patients had increased exhaustibility breathlessness and palpitations on mild effort, and 5 of them also suffered from precordial pain in association with the palpitations. One woman

TABLE 3. Distribution of some commonly recorded symptoms before operation according to age groups and function classes.

Age group	No. of patients	Function class	No. of patients	Symptoms: Increased exhaustibility	Breathlessness	Palpitations	Precordial pain
A	50	II	9	9	9	—	—
B	29	II	13	11	13	4	1
C	28	II	16	16	16	5	1
		III	6	6	6	6	5
Total	107		44	42	44	15	7

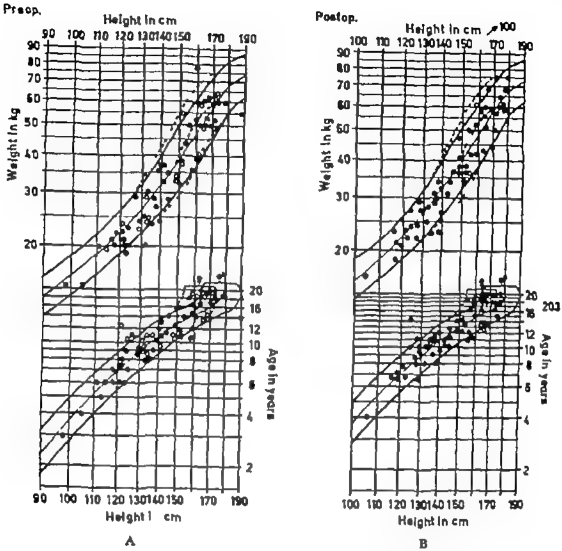
TABLE 4. Circumstances associated with the discovery of the heart disease distributed according to age groups.

Occasion		Age group A	B	C	Total
Public health examination	Child Welfare Clinic	12	4	—	16
	At school	19	11	8	38
	Mass radiography	3	5	2	10
	During pregnancy	—	—	9	9
Other health examination		—	3	2	5
					78
Examination for non-cardiac disease	Bronchitis	4	—	1	5
	Other infections	4	—	1	5
	Other diseases	7	4	3	14
					24
Examination for cardiac symptoms	Dyspnoea	—	1	1	2
	Tachycardia	—	1	1	2
	Precordial pain	—	—	1	1
					5

of age group C had precordial pains of a suspected angina pectoris type. One patient in function class III, with pulmonary hypertension, was slightly cyanotic.

In only 14 children were recurrent infections of the upper respiratory tract observed. In the adults there appeared to be no increase in tendency to infection.

Murmurs had been detected during the first year of life in only 10 cases. In [illegible] patients the murmur was discovered



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been subjectively free of symptoms preoperatively but deteriorated, 3 of them due to postoperative cardiac rhythm disturbances and one woman due to an abnormal increase in weight.

Exercise tests. Exercise tests were performed mainly so as to allow comparison between the physical work capacity before and after operation, but also to obtain an idea of the relationship between subjective symptoms, and objective signs of functional reduction. Exercise tests were performed by 81 patients preoperatively and by 69 at the follow-up examination.

In 68 patients comparison was made between the preoperative and postoperative values of PWC_{170}, expressed in kpm/min per kg body weight (Fig. 4) but no significant difference was noted either in the children or adults.

Preoperatively 11 patients in function class II were assessed as having a normal physical work capacity and in 9 patients in function class I this was assessed as reduced. Since breathlessness was a common symptom, it was expected that patients with a reduced physical work capacity would have a higher than normal respiratory rate in relation to the work load. This was in fact shown in only 6 patients, for whom the exercise tests were discontinued at relatively low work loads because of a high respiratory rate. In these patients lung function tests gave values within the normal limits.

In 15 patients in function class II with reduced physical work capacity there were signs of limitation of peripheral blood flow after a short period of low work load, when the pulse and respiration values were relatively high,

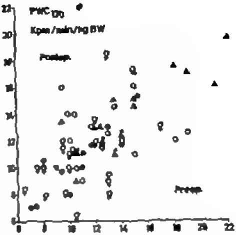

Fig. 4. Physical work capacity expressed in kpm/min per kg body weight, before and after operation.

Circles represent women, triangles men; open symbols = children, filled symbols = patients in age group B. Circles with crosses, and triangles with arrows represent patients in age group C.

the patient was forced to discontinue the exercise test because of tiredness, especially of the legs. Muscular weakness, due for example, to lack of training, may have been contributory.

Postoperatively 16 patients in function class I were assessed as having a reduced physical work capacity.

In 22 patients who had been subjectively symptom-free preoperatively there was a marked subjective improvement in the work capacity but no objective functional change at the follow-up examination.

Other investigations

Blood. In all patients except three the preoperative values for red blood cells, haemoglobin, haematocrit and sedimentation rate lay within the normal limits,

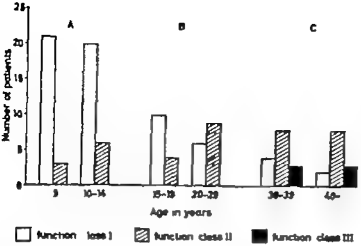

Fig 3. No. of patients in different function classes according to age groups at time of operation.

during the pre school years. In 43 patients the murmur was discovered during the school period, at an age of between 7 and 14 years. In 10 out of 28 patients in age group C the murmur was detected after the age of 30 years.

In consideration of the age distribution of the material, it was also of interest to know how the heart disease had been discovered. As shown in Table 4 the discovery was usually made during a routine examination at a Child Welfare Clinic or at school or at mass radiography an examination during pregnancy or other routine health investigations. In 78 patients the heart disease was discovered at examinations of this type. In 24 patients a murmur had been heard during the investigation of another condition. Only 5 patients had sought medical advice for symptoms which could be related to heart disease.

Functional capacity and exercise tests

Function classes The functional capacity of the patient was evaluated on the basis of the case-history data.

The *preoperative* function classes in relation to the age groups are given in Fig 3 In age group A, 41 out of 50 children were completely free of symptoms (function class I) 9 patients were assigned to function class II because of increased exhaustibility and breathlessness on moderate effort. In age group B, consisting of 29 patients of ages 15—29 years, 16 of these patients were in function class I and 13 in function class II. Out of 28 patients in age group C, only 6 were free of symptoms (function class I) 16 patients were in function class II and 6 in function class III

The functional reduction began at the age of about 20 years 51 out of 64 patients below 20 years of age were in function class I compared with only 12 out of 43 patients over this age.

At the *follow-up examination* a marked improvement of the subjective functional capacity was noted. Only 8 patients now qualified for function class II one in age group A, 3 in age group B and 4 in age group C. One of these patients in function class II showed no change and 3 patients in preoperative function class III showed improvement. 4 patients had

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In 15 patients in function class II with reduced physical work capacity there were signs of limitation of peripheral blood flow after a short period at a low work load, when the pulse and respiration values were relatively high, the patient was forced to discontinue the exercise test because of tiredness, especially of the legs. Muscular weakness, due, for example, to lack of training, may have been contributory

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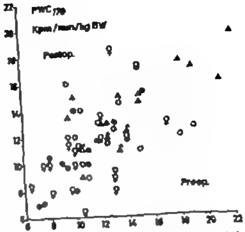

Fig. 4. Physical work capacity expressed in kpm/min per kg body weight, before and after operation.

Circles represent women, triangles men; open symbols = children, filled symbols = patients in age group B. Circles with crosses, and triangles with arrows represent patients in age group C.

according to the norm used at our laboratory (de Verdier and Killander 1965) these exceptions were two children and one adult with somewhat low blood values indicating mild anaemia. At the follow up examination the routine blood values were normal in all patients.

Urine analysis. Tests for protein and glucose and sediment determination, were performed as routine, and the results were normal in all patients both preoperatively and at the follow-up examination.

The non protein nitrogen was determined before and after the operation and was normal in all patients.

The *basal metabolic rate* was determined in all adult patients, with normal results. In no case was there any clinical sign of dysfunction of the thyroid gland, either before or after the operation.

Lung function tests The normal values were calculated according to the norm used at this laboratory The following variations from the mean values were considered normal for MVV_f and VC $\pm$ 20 % for FEV % $\pm$ 8 % (see Hallén 1964 for further references) 36 patients were examined preoperatively including 6 children, and these results lay within the normal limits.

At the follow-up examination lung function tests were carried out in a further 10 patients, with normal results.

Electroencephalogram (EEG) EEG recordings were made preoperatively in 92 patients, and in 83 of them the results were evaluated as normal In 3 children and 1 adult, the EEG was of a paroxysmal type. In 5 patients (3 children and 2 adults) other non-specific pathological changes were noted.

At the follow-up examination EEG recordings were made in 97 patients. The pathological changes recorded before the operation were still present. In 5 patients who had shown a normal EEG preoperatively non-specific pathological changes were now seen, which in two cases appeared to be related to suspected postoperative cerebral air emboli in the other three patients no definite explanation for the EEG change was found.

Discussion

The results of the preoperative height and weight determinations are in agreement with those of previous similar Scandinavian investigations of Kjellberg et al. (1959) and Davidsen (1960) Taussig (1947) pointed out that children with an atrial septal defect are often gracile, thin and underdeveloped, but according to Kjellberg et al. this feature is to be seen also in children with a large left to-right shunt via a ventricular septal defect or a patent ductus arteriosus. Although only a few patients showed weight values outside the normal range limits ($\pm$ SD) there was some tendency in the children towards low weights preoperatively At the follow up examination they showed a more normal distribution around the mean value In some patients, however the weight was lower than normal before operation as well as at the follow up examination, in spite of a normal weight increase, and this would seem to indicate that in addition to haemodynamic factors other for example constitutional factors may also

provide a reason for the slender body build which may sometimes be found in patients with an atrial septal defect.

It is to be expected that a congenital disease such as atrial septal defect of the secundum type, with its often rather mild physical manifestations, will be discovered relatively late in life. In many cases in the present series a murmur was heard on some occasion during school years, but was not regarded as a sign of organic heart disease, but was often "rediscovered" at a later examination or in connection with the onset of symptoms. The onset of the symptoms and the symptoms themselves differed somewhat in the present series from the descriptions usually given by other authors, including Bedford et al. (1957) and Davidsen (1960), but this may be explained by the fact that, with a few exceptions, this happened to be a series of haemodynamically uncomplicated secundum defects with mild symptoms and a late onset. Mild symptoms occurred in 44 out of 107 patients, and in only 6 cases were the symptoms so pronounced as to indicate function class III. together with the finding that the symptoms were seldom manifest before the age of 20 years, the present results are probably representative of the haemodynamically uncomplicated secundum defect.

When grading the functional capacity into function classes according to the degree of severity of the symptoms as reported in the case history consideration must be taken of the possible presence of non-cardiac symptoms and also of cardiac symptoms which are not necessarily due primarily to the atrial septal defect but which arise rather from some secondary deterioration of the basic general condition. For example, if the patient has been aware of his murmur since childhood, and has often been advised to avoid undue effort (e.g. has been excused from gymnastics, etc.) this may result in a reduction of his general physical fitness and thus a lowering of his physical work capacity. This may be less pronounced in patients in whom an atrial septal defect is diagnosed during a routine examination at a more advanced age. At the same time it must be taken into account that patients with a congenital heart disease such as ASD sec may become so adapted to their condition that they consider themselves free from symptoms. With a functional improvement after the operation the patient may then realise the falsity of his previous assumption. Further, a subjective improvement after the operation, which is not accompanied by any objective change, may be a nonspecific expression of the reaction of the patient to successful surgery. No objective evaluation of the functional capacity after surgical repair of atrial septal defects appears to have been reported previously. In the present series there was a number of patients before as well as after the operation with a reduced physical work capacity, but preoperatively most of the patients had symptoms, while postoperatively the majority were subjectively symptom-free, and this shows the value of objective function tests in assessing the physical work capacity of the patient. After operation on an uncomplicated ASD sec, an improvement of the physical work capacity might be expected. This capacity is governed

mainly by the capacity of the circulatory system to transport oxygen (Sjöstrand 1956) In patients with a low physical work capacity preoperatively due to reduced peripheral blood flow probably resulting from lack of physical training, closure of the defect in uncomplicated cases should not *a priori* be followed by any change in the systemic circulation and therefore in the physical work capacity Thus was analysed in the present series, and no significant change in the physical work capacity was noted after the operation. Jonsson et al. (1957) have demonstrated further that there is no relationship between magnitude of shunt and physical work capacity

The ventilation capacity in those patients in whom this was tested lay within the normal limits, with no difference between the pre- and postoperative values. These patients also showed preoperatively only a slight raise in the systolic pressure in the pulmonary artery and a low pulmonary resistance at rest. On the other hand in atrial septal defect with a high systolic pressure in the pulmonary artery regardless of whether this was caused by a greatly increased pulmonary blood flow or a raised pulmonary resistance, Woolf (1963) found signs of low compliance and high non-elastic resistance as an explanation for the "excessive hyperventilation" on exercise, while Gazetopoulos and Davies (1966) found no relationship between different haemodynamic parameters and excessive ventilatory rate during exercise in patients with left to-right shunts, but discuss the possibility of a relationship betwen tissue hypoxia and ventilatory response.

In order to evaluate any cerebral anoxic damage associated with the operation, electroencephalographic recordings were made before the operation and at the follow up examination. None of the patients showed clinico-neurological signs of cerebral dysfunction at the follow-up examination. In three patients, for whom both the operation and the post operative period were free of complications, newly manifest nonspecific pathological changes were seen, for which no definite explanation was found.

Summary

The growth and physical development in 66 patients below the age of 20 years is reported. In only a few patients did the preoperative values lay outside the ± 2 SD limits of variation for Swedish children, which is in agreement with previous findings. In the children, however there was some tendency to low weights preoperatively but at the follow up examination a weight increase was noted, the deviation from the mean value diminishing significantly this can be interpreted as a nonspecific sign of improvement in this age group.

The murmur was usually discovered at a routine examination during the preschool or school period. Only 5 of the 107 patients had sought medical advice for symptoms which could be related to the cardiac disorder

Preoperatively 44 patients had symptoms, 38 in function class II and 6 in function class III The functional deterioration occurred after the age of 20 years. Reduction in physical work capacity probably due to lack of physical

training, was noted as an average result preoperatively and was unchanged postoperatively. Postoperatively there was, however subjective improvement in the work capacity which may have been an expression of the general nonspecific reaction after the operation.

There was no postoperative change in the physical work capacity as expressed in PWC_{170}, compared with the preoperative values.

Lung function tests in 36 patients gave normal results both pre- and postoperatively.

No signs of cerebral anoxic damage were found by EEG or clinico-neurological routine examination after the operation.

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After operation. In the immediate postoperative period auscultation showed the second sound to be *still constantly* split in 72 patients, and the pulmonary component was accentuated in 90 patients.

On PCG recording, however the splitting was *found to* show some physiological variation in 45 patients. The interval between the sound components had decreased somewhat, compared with the preoperative findings, being 4.6 (2—7) csec, on the average with no difference between the age groups. The pulmonary component was accentuated in 36 patients.

At follow-up examination. On auscultation the second sound at the follow-up examination was variable in 64 patients and the pulmonary component was accentuated in [illegible] patients.

PCG recording, however showed a definitely inconstant splitting of the second sound in 97 patients, where the time interval between the sound components varied by 1—2 csec. The time interval between the aortic and pulmonary components was now on the average, 5.0 (3—8) csec. *In* 34 patients, including 18 children, the pulmonary component was accentuated.

Thus before the operation constant splitting of the second sound was registered in 96 of the 107 patients, while at the follow-up examination the splitting of the sound varied *during the respiratory* cycle by 1—2 csec in a similar number of cases. The relationship between the amplitudes of the sound components also varied. Of the 34 patients in whom a residual predominant pulmonary component was found at follow-up

TABLE 5. Second heart sound on PCG registration before and after operation and at follow-up examination. Time interval in csec between aortic (A_2) and pulmonary (P_2) components of the second heart sound on expiratory phase.

	Second heart sound			
	Split		Amplitude $P > A_2$	Time interval
	constant	inconstant		
	No.	No.	No.	csec
Preop.	96	11	60	5.5 (3—8)
Postop.	62	45	36	4.6 (2—7)
Follow-up	10	97	34	5.0 (3—8)

examination, 18 were children. PCG recording was superior to auscultation as regarded the evaluation of the amplitude of the sound components and the variations in time interval between the aortic and pulmonary components of the second sound.

Third heart sound. In 19 cases, including 13 children, a diastolic extra sound was heard.

This sound was always recorded together with a diastolic filling murmur in patients with a large left-to-right shunt, and was *interpreted as a diastolic* filling sound. This appeared to be absent after the operation.

Systolic murmurs. Table 6 shows the incidence of systolic murmurs heard on auscultation at the three examinations.

Before operation. In 73 patients the systolic murmur was *of intensity* grade III, with an equal distribution between

CHAPTER V

Physical cardiac findings and chest roentgenogram before and after operation

Precordial palpation

Preoperatively there were palpatory signs of increased activity of the right ventricle in 76 patients. At the *postoperative* examination some normalization of these findings was observed the right ventricular activity being considered increased in only 27 patients, 18 of whom were children. Obviously no close correlation between palpatory findings and haemodynamic conditions can be made, but the present results may indicate some relationship between the change in palpatory findings and the decreased load on the right ventricle.

Auscultation and phonocardiogram

The first heart sound was evaluated over the 4th left intercostal space, parasternally and the second sound and systolic murmur over the pulmonary area (2nd and 3rd left intercostal spaces parasternally) The diastolic extra sounds and murmurs were evaluated over the tricuspid area (4th left intercostal space, parasternally or midsternally) The second sound and systolic murmur were also evaluated during the more immediate postoperative period at about 2 weeks after the operation Separate evaluation of the aortic and pulmonary components of the second sound may be difficult The criterion used for an accentuated pulmonary component was that its distribution over the precordium should be increased to regions outside the customary pulmonary area, especially if in such regions the pulmonary component was of greater amplitude than the aortic component.

First heart sound Preoperatively the first heart sound was considered to be louder than normal in 43 patients, with an approximately equal distribution between children and adults.

At the *follow-up* examination this heart sound was considered normal in all except 12 cases.

Second heart sound. Table 5 shows the results of evaluation of the second sound in the entire series before and also immediately after the operation and at the follow up examination.

Before operation On auscultation constant splitting of the second sound was found in all cases, and accentuation of pulmonary component in all except 5

On PCG recording the time interval between the aortic and pulmonary components of the second sound was found to be constant in all patients except 11 and was, on the average 5.5 (3—8) *centiseconds (csec) No difference* was seen between the different age groups. In the 11 patients in whom the second sound varied with respiration, the interval variation between the sound components was less than 1 csec. The pulmonary component was accentuated in 60 patients.

After operation. In the immediate postoperative period auscultation showed the second sound to be still constantly split in 72 patients, and the pulmonary component was accentuated in 90 patients.

On PCG recording, however the splitting was found to show some physiological variation in 45 patients. The interval between the sound components had decreased somewhat, compared with the preoperative findings, being 4.6 (2—7) csec, on the average with no difference between the age groups. The pulmonary component was accentuated in 36 patients.

At follow-up examination. On auscultation the second sound at the follow-up examination was variable in 64 patients and the pulmonary component was accentuated in 93 patients.

PCG recording, however showed a definitely inconstant splitting of the second sound in 97 patients, where the time interval between the sound components varied by 1—2 csec. The time interval between the aortic and pulmonary components was now on the average, 5.0 (3—8) csec. In 34 patients, including 10 children, the pulmonary component was accentuated.

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	Split		Amplitude	Time interval
	constant	inconstant	$P > A_2$	
	No.	No.	No.	csec
Preop.	96	11	[illegible]	5.5 (3—8)
Postop.	62	45	36	4.6 (2—7)
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TABLE 6. Incidence of patients with systolic murmurs of different grades heard on auscultation before and after operation and at follow-up examination.

	Systolic heart murmur grade IV	III	II	I	0
Preop.	13	73	19	2	—
Postop.	—	3	40	41	23
Follow up	—	2	38	57	10

children and adults. A systolic murmur of grade II was found in 19 patients, and of grade IV in 13 patients. In two adult patients a systolic murmur of grade I was heard.

After operation. After the operation the systolic murmur was attenuated and in only 3 patients was it of intensity grade III Systolic murmurs of grade II were heard in 40 patients, the majority being children. A low pitched grade I systolic murmur was heard in 41 patients, while in 23 patients no murmur at all was heard

At follow-up examination At the follow up examination a systolic murmur of grade III was heard in 2 patients. A systolic murmur of grade II was heard in 38 patients, this figure thus being essentially unchanged compared with the immediately postoperative findings. On the other hand a systolic murmur of grade I was now somewhat more frequent, being heard in 57 patients.

The PCG recording was in essential agreement with the auscultatory findings except in three patients, in whom murmurs of grade I were heard on auscultation but were not confirmed by PCG Before and after operation the murmur was of the early systolic ejection type, but postoperatively both the amplitude and intensity were lower and the duration usually somewhat shorter

Diastolic murmur preoperative The typical early mid-diastolic filling murmur was only heard before the operation, and then in 60 patients.

The PCG recording was in agreement preoperatively with the auscultatory findings regarding the distribution and intensity of the systolic murmur but on the other hand in 5 cases a diastolic murmur definitely heard on auscultation was not registered by PCG

Systemic blood pressure

The arterial blood pressure was measured by the usual cuff method, with an aneroid manometer checked against a mercury column.

The mean preoperative value for children was 110/70 (range 95/60—130/85) and this value remained essentially unchanged after the operation. Two adult patients had arterial hypertension with systolic pressures of 185 and 200 mm Hg and diastolic pressures of 100 mm Hg The mean preoperative value for adults was 135/80 (range 105/60—200/100) and this value remained essentially unchanged at the follow up examination (140/85 range 110/65—200/100)

Chest roentgenogram

Since it is often difficult to evaluate the *heart configuration* in patients with atrial septal defects, no detailed analysis or gradation of the different findings was made

Preoperatively it was noted, however that 82 patients had distinct dilatation

TABLE 7 Distribution of patients according to heart size as determined by chest X-ray before and after operation.

Heart size			No.	
			Preop.	Postop.
Normal	Children	<350 ml/m² BSA	[illegible]	23
	Women	<450	14	[illegible]
	Men	<500	2	6
		Total	21	60
Slight enlargement	Children	>350—500	33	26
	Women	>450—600 »	19	[illegible]
	Men	>500—650	[illegible]	6
		Total	58	38
Moderate enlargement	Children	>500—650	10	1
	Women	>600—750 »	7	5
	Men	>650—800	4	—
		Total	21	6
Pronounced enlargement	Children	>650	2	—
	Women	>750	4	2
	Men	>800	1	1
		Total »	7	3

of the pulmonary artery and its central and peripheral branches. In 76 of these patients signs of enlargement of the right ventricle were seen, which in 36 cases were evaluated as pronounced. In 18 patients only moderate dilatation of the pulmonary artery was seen, and in 7 patients the configuration was considered to be normal.

At the *follow-up examination* a regression of the preoperatively increased dilatation of the central and peripheral branches of the pulmonary artery was seen. Residual dilatation of the main trunk of the pulmonary artery was observed in 81 patients; this dilatation was considered to be less pronounced than before the operation but more pronounced than the normal. In 28 patients the configuration was normal. Neither the age of the patient nor the length of time after operation appeared to influence the degree of residual dilatation of the main trunk of the pulmonary artery.

Heart volume. The results of the evaluation of the relative heart volume before the operation and at the follow-up examination are given in Table 7.

Preoperatively the heart volume was normal in 21 patients. In 58 patients there was slight enlargement of the heart, in 21 patients moderate enlargement and in only 7 patients pronounced enlargement. Preoperatively the heart volume was, on the average, 448 (315—

800) ml/m² BSA in children, 491 (325—800) ml/m² BSA in young adults and 625 (400—1260) ml/m² BSA in older adults.

At the *follow up examination* the corresponding values were 350 (240—510) 419 (260—760) and 554 (430—1260) ml/m² BSA. In the patients of all age groups the roentgenological heart volume was significantly (***) smaller postoperatively than preoperatively

Sixty patients now showed a normal heart volume and 38 a slight residual cardiac enlargement. Only 9 patients had more advanced cardiac enlargement (6 moderate and 3 pronounced) In 1 child and 3 women with residual, moderate enlargement this could be explained by postoperative cardiac rhythm disturbances viz. an AV block II in three cases, and an AV block III in one case. In the other 2 cases no explanation was found for the absence of volume reduction 2 1/2 years, on the average after the operation.

Three patients had residual pronounced cardiac enlargement at the follow-up examination. In these three patients the enlargement was probably an expression of irreversible dilatation due to myocardial damage, which had been caused preoperatively by pulmonary hypertension in one case and by myocarditis with mitral insufficiency in an other case. The third patient had atrial fibrillation both pre- and postoperatively

Discussion

The preoperative physical cardiac findings in this series of patients were in agreement with those usually described previously in uncomplicated atrial septal defect of the secundum type. The post operative findings were as expected after a satisfactory operation. Postoperative findings have been described by Loogen & Toker (1961) among others, but the value of their findings in 100 surgically repaired secundum defects is limited somewhat by the fact that only 43 of the patients underwent recatheterization, 7 of whom had a residual shunt. The present material consisted of a haemodynamically uncomplicated uniform series of surgically corrected ASD sec, in which, at follow up examination with heart catheterization it was shown that the defect was completely closed.

After repair of an atrial septal defect, the excess volume load on the right heart and pulmonary circulation disappears instantly while on the other hand structural restitution occurs gradually As a result a flow murmur can be heard over the pulmonary region, caused by turbulent flow through a still somewhat dilated pulmonary artery This means also that the second sound, partly for the same reason — reduced elasticity in the wall of the pulmonary artery (Jonsson, 1958) — is still extensively split but with some physiological variation which can be explained by a decrease in the flow volume.

In this series of patients the total number of residual murmurs was essentially greater than that reported by Loogen & Toker (1961) and Reindell et al. (1962) while, on the other hand, the frequency of murmurs of grade II was essentially the same. However a larger number of weak murmurs (grade I) were heard on auscultation.

Preoperatively 21 patients showed a normal heart olume roentgenologically while only 7 were considered to have a normal heart configuration. Dilatation of the pulmonary artery and increased vascularity of the lungs do not occur only in atrial septal defect, but these conditions without dilatation of the left atrium appear to constitute the most definite roentgenological finding

Roentgenologically compared with the preoperative findings reduced vascularity of the lungs was the first change observed after the operation, while on the other hand the main trunk of the pulmonary artery and right entricle may return to normal gradually during the year immediately following surgery Loogen & Toker (1961) found a residual cardiac enlargement in 34 % usually in older patients. In the present series a slight residual cardiac enlargement was seen roentgenologically in 38 patients (35 %) of whom 26 were children. The large proportion of children can probably be explained by the fact that they ere examined, on the average, sooner after the operation than the adults. At the routine examination 1 1/2 years, on the erage after recatheterization, only 2 children showed a residual slight cardiac enlargement, which in one of them could ha e been due partly to preoperati rheumatic carditis. In most cases, however the pulmonary artery was somewhat dilated compared with normal conditions. The relationship between age heart olume, left-to-right shunt and right entricular pressure will be discussed in chapter VII.

Slight residual cardiac enlargement did not gi rise, however to any abnormal haemodynamic changes. In isolated cases with more pronounced enlargement after the operation, this was due either to newly acquired postoperative, or irreversible preoperative factors.

Summary

The physical findings before and after operation in this series were in agreement with previous findings in uncomplicated ASD sec.

The second heart sound was preoperatively constantly split and postoperatively t was inconstantly split in 90 % of the patients, but the average time interval between the sound components was practically unchanged, viz. 5—6 csec

Systolic murmurs were heard postoperati ely in all except 10 patients, but were of a lower grade than preoperatively and can be explained by turbulent flow in the dilated pulmonary artery

All patients except 2 adults had a normal arterial blood pressure before the operation, and this remained unchanged postoperatively

The heart configuration was pathological preoperatively in all except 7 patients, with dilatation of the pulmonary artery and its central and peripheral branches. Signs of hypertrophy of the right ventricle were seen in 76 cases. Postoperatively the vascularity of the lungs was reduced compared with preoperatively while the dilatation of the main trunk of the pulmonary artery persisted for a long period and was seen in 81 of the 107 patients at the follow-up examination, though to a less pronounced extent than preoperatively

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Three patients had residual pronounced cardiac enlargement at the follow up examination. In these three patients the enlargement was probably an expression of irreversible dilatation due to myocardial damage, which had been caused preoperatively by pulmonary hypertension in one case and by myocarditis with mitral insufficiency in another case The third patient had atrial fibrillation both pre- and postoperatively

Discussion

The preoperative physical cardiac findings in this series of patients were in agreement with those usually described previously in uncomplicated atrial septal defect of the secundum type. The postoperative findings were as expected after a satisfactory operation. Postoperative findings have been described by Loogen & Toker (1961) among others, but the value of their findings in 100 surgically repaired secundum defects is limited somewhat by the fact that only 43 of the patients underwent recatheterization, 7 of whom had a residual shunt. The present material consisted of a haemodynamically uncomplicated uniform series of surgically corrected ASD sec, in which, at follow up examination with heart catheterization, it was shown that the defect was completely closed.

After repair of an atrial septal defect, the excess volume load on the right heart and pulmonary circulation disappears instantly while on the other hand structural restitution occurs gradually As a result a flow murmur can be heard over the pulmonary region, caused by turbulent flow through a still somewhat dilated pulmonary artery This means also that the second sound, partly for the same reason — reduced elasticity in the wall of the pulmonary artery (Jonsson, 1958) — is still extensively split but with some physiological variation, which can be explained by a decrease in the flow volume

In this series of patients the total number of residual murmurs was essentially greater than that reported by Loogen & Toker (1961) and Reindell et al. (1962) while, on the other hand, the frequency of murmurs of grade II was essentially the same However a larger number of weak murmurs (grade I) were heard on auscultation.

Electrocardiographic findings before and after operation

ECG studies were made in all 107 patients both preoperatively and at the follow-up examination, with regard to rate and rhythm, the nature and duration of the P wave and the QRS complex, the direction of the mean QRS axis in the frontal plane, and T wave abnormalities. In addition, the ECG was studied with respect to arrhythmia and S-T and T changes during the immediate postoperative period.

Heart rate and rhythm

Preoperatively the heart rate was, on the average, 93 (70—150) beats per minute in the children and 78 (55—115) in the adults. In 20 children and 3 adults the heart rate was more than 100 beats per minute.

At the *follow-up* examination the corresponding figures were 81 (45—130) and 71 (40—120) respectively. Five children and 2 adults now had a heart rate of more than 100 beats per minute.

Preoperatively all patients showed *sinus rhythm* with the exception of one 62-year old woman with atrial fibrillation with a normal ventricular rate.

At the *follow-up* examination 5 patients showed residual postoperative arrhythmia. Three patients had an A V block II in two of these patients this persisted at a later examination, but in the third patient, a 12 year old girl, sinus rhythm was recorded 4 years after the operation. One patient had a postoperative A V block III which required pacemaker therapy and another patient showed therapy-resistant atrial fibrillation which had been present preoperatively.

Cardiac rhythm disturbance during the immediate postoperative period. During the entire postoperative period up to the follow-up examination, 50 patients showed sinus rhythm, the incidence being somewhat higher in young than in older patients.

In 30 patients, relatively regular supra ventricular rhythm was noted initially and on an average of 2.3 days after the operation this changed to regular sinus rhythm.

In 6 patients, sinus rhythm was recorded during the first 24 hours postoperatively and after an average of 4.1 days this changed to supraventricular rhythm, but 3.5 days later sinus rhythm was again noted in these patients.

Thus 86 of the 107 patients had regular sinus rhythm 8 days after the operation, while 21 patients showed residual postoperative arrythmia. Of these, 12 patients (5 children, and 7 adults) had regular supraventricular rhythm, which changed to sinus rhythm after an average of 29 days. 5 patients (2 children and 3 adults) showed an A V block

Preoperatively 21 patients had a normal heart volume 58 patients showed slight cardiac enlargement 21 moderate enlargement and 7 pronounced enlargement. At the follow up examination 60 patients had a normal heart volume, 38 patients showed slight cardiac enlargement and in 9 patients the enlargement was more pronounced. There was a significant (***) postoperative reduction of the heart volume in the different age groups. The children in particular showed a residual slight enlargement which may be explained by the fact that in this group the observation period was shorter than in the adults at a further follow up examination 18 months, on the average, after recatheterization, the heart volume was normal in all children except three. No abnormal haemodynamic changes were noted in association with residual slight enlargement. In the isolated cases with more pronounced cardiac enlargement postoperatively this was due either to newly acquired postoperative, or irreversible preoperative conditions.

TABLE 8. Distribution of preoperative QRS complex in lead V_1 in relation to age group, heart size, shunt group and right ventricular systolic pressure.

Age group	R No.	R %	rSR No.	rSR %	rsr No.	rsr %	rS No.	rS %
A	14	61	19	40	9	47	8	[illegible]
B	5	22	12	25	7	37	5	34
C	4	17	17	35	3	16	2	13
Total	23	100	48	100	19	100	15	100

Heart size	R No.	R %	rSR No.	rSR %	rsr′ No.	rsr′ %	rS No.	rS %
Normal	3	14	6	13	4	21	4	27
Slight enlargement	16	73	25	54	8	42	8	[illegible]
Moderate enlargement	2	9	11	24	6	31	2	13
Pronounced enlargement	1	4	4	9	1	6	1	7
Total	22	100	46	100	19	100	15	100

Shunt group	R No.	R %	rSR No.	rSR %	rsr No.	rsr %	rS No.	rS %
1	4	18	6	13	4	21	3	[illegible]
2	11	50	17	37	8	42	8	53
3	7	32	23	50	7	37	4	27
Total	22	100	46	100	19	100	15	100

RV systolic pressure mm Hg	R No.	R %	rSR No.	rSR %	rsr's No.	rsr's %	rS No.	rS %
30	8	36	20	43	7	38	6	40
> 30	14	[illegible]	26	57	12	[illegible]	9	60
Total	22	100	46	100	19	100	[illegible]	100

QRS complex

In spite of large variations in the QRS complex in lead V_1, it was possible in principle to classify the different types into the four QRS patterns shown in

Fig. 5. Configuration of QRS complex in lead V_1

II In 3 of these patients sinus rhythm was recorded 3 weeks, 4 months and 4 years, respectively after the operation, but in the other 2 patients this block is still present. One 42 year old woman had a postoperative A V block III which necessitated pacemaker therapy Two patients had atrial fibrillation, which after medication altered to sinus rhythm 8 weeks and 12 weeks, respectively after the operation. In the patient who had atrial fibrillation preoperatively repeated attempts to regularize the residual postoperative fibrillation, both by medication and cardioversion, were unsuccessful.

A detailed study of different data obtained during the operation under hypothermia was made in an attempt to determine the reason for the immediate postoperative arrhythmias, but these showed no correlation with the operation time, time of circulatory arrest, cooling or rewarming time, or with the acid base values. In association with inflow occlusion all patients showed cardiac rhythm disturbances of varying types, usually nodal rhythm with ectopic ventricular beats, but there was no apparent relationship between these disturbances and the residual arrhythmias. A *tendency* was observed, however to immediate postoperative arrhythmia in patients with large central defects, and, especially those with low defects, where traumatic effects on the atrio-ventricular nodal region were often unavoidable.

P waves

Preoperatively the amplitude of the P wave, measured in mm (1 millivolt, mV = 10 mm) in *lead II* was, on the average, 1.5 in the children and 1.2 in the adults.

Postoperatively the corresponding values were 1.2 and 1 1 mm respectively Only in the children was there a significant difference (***) between the pre and postoperative values.

The *amplitude* of the P wave in *lead* V_1 was, on the average, somewhat lower both pre and postoperatively (1 0 and 0 6 mm, respectively) than in lead II but the postoperative amplitude reduction in lead V_1 was more pronounced (***)

Preoperatively the duration of the P wave in *lead II* was, on the average, 7.5 csec in the children and 8.7 in the adults.

Postoperatively the corresponding values were 6.5 and 7 7 csec, respectively The difference between the pre and postoperative values were significant for the children (***) and for the adults (**)

Only in 6 patients were preoperative signs of atrial hypertrophy observed in lead II with a P wave amplitude of 2 5 mm or more or a P wave duration of 12 csec or more.

P R interval Preoperatively the P R interval was, on the average, 15 6 csec, and at the *follow-up* examination this was significantly shorter (**) viz. 14.2 csec. The P R interval was longer than 20 csec in 13 patients (including 10 in age group C) preoperatively and in 9 patients at the follow-up examination. On the average, the adult patients showed a somewhat longer P R interval than the children.

Table 8 *Distribution of preoperative QRS complex in lead V in relation to age group, heart size, shunt group and right ventricular systolic pressure.*

Age group	R No.	R %	rSR No.	rSR %	rsr No.	rsr %	rS No.	rS %
A	14	61	19	40	9	47	8	53
B	5	22	12	25	7	37	5	34
C	4	17	17	35	3	16	2	13
Total	23	100	48	100	19	100	15	100
Heart size	**R No.**	**R %**	**rSR No.**	**rSR %**	**rsr' No.**	**rsr' %**	**S No.**	**S %**
Normal	3	14	6	13	4	21	4	27
Slight enlargement	16	73	25	54	8	42	8	[illegible]
Moderate enlargement	2	9	11	24	6	31	2	13
Pronounced enlargement	1	4	4	9	1	6	1	7
Total	22	100	46	100	19	100	15	100
Shunt group	**R No.**	**R %**	**SR No.**	**SR %**	**rsr No.**	**rsr %**	**rS No.**	**rS %**
1	4	18	6	13	4	21	3	20
2	11	50	17	37	8	42	8	53
3	7	32	23	50	7	37	4	27
Total	[illegible]	100	46	100	19	100	15	100
RV systolic pressure mm Hg	**R No.**	**R %**	**SR No.**	**SR %**	**rsr No.**	**rsr %**	**rS No.**	**rS %**
50	8	36	20	43	7	38	6	40
> 50	14	64	26	57	12	62	9	60
Total	22	100	46	100	19	100	15	100

QRS complex

In spite of large variations in the QRS complex in lead V_2, it was possible in principle to classify the different types into the four QRS patterns shown in

Fig. 3. Configuration of QRS complex in lead V

II. In 3 of these patients sinus rhythm was recorded 3 weeks, 4 months and 4 years, respectively, after the operation, but in the other 2 patients this block is still present. One 42 year old woman had a postoperative A-V block III which necessitated pacemaker therapy. Two patients had atrial fibrillation, which after medication altered to sinus rhythm 8 weeks and 12 weeks, respectively, after the operation. In the patient who had atrial fibrillation preoperatively, repeated attempts to regularize the residual postoperative fibrillation, both by medication and cardioversion, were unsuccessful.

A detailed study of different data obtained during the operation under hypothermia was made in an attempt to determine the reason for the immediate postoperative arrhythmias, but these showed no correlation with the operation time, time of circulatory arrest, cooling or rewarming time, or with the acid base values. In association with inflow occlusion all patients showed cardiac rhythm disturbances of varying types, usually nodal rhythm with ectopic ventricular beats, but there was no apparent relationship between these disturbances and the residual arrhythmias. A tendency was observed, however, to immediate postoperative arrhythmia in patients with large central defects, and especially those with low defects, where traumatic effects on the atrio-ventricular nodal region were often unavoidable.

P waves

Preoperatively the amplitude of the P wave, measured in mm (1 millivolt, mV = 10 mm) in *lead II* was, on the average, 1.5 in the children and 1.2 in the adults.

Postoperatively the corresponding values were 1.2 and 1.1 mm respectively. Only in the children was there a significant difference (***) between the pre- and postoperative values.

The *amplitude* of the P wave in *lead V_1* was, on the average, somewhat lower both pre- and postoperatively (1.0 and 0.6 mm, respectively) than in lead II, but the postoperative amplitude reduction in lead V_1 was more pronounced (***).

Preoperatively the duration of the P wave in *lead II* was, on the average, 7.5 csec in the children and 8.7 in the adults.

Postoperatively the corresponding values were 6.5 and 7.7 csec, respectively. The difference between the pre- and postoperative values were significant for the children (***) and for the adults (**).

Only in 6 patients were preoperative signs of atrial hypertrophy observed in lead II with a P wave amplitude of 2.5 mm or more or a P wave duration of 12 csec or more.

P-R interval. Preoperatively the P-R interval was, on the average, 15.6 csec, and at the *follow-up* examination this was significantly shorter (**), viz. 14.2 csec. The P-R interval was longer than 20 csec in 13 patients (including 10 in age group C) preoperatively and in 9 patients at the follow-up examination. On the average, the adult patients showed a somewhat longer P-R interval than the children.

TABLE 8 Distribution of preoperative QRS complex in lead V in relation to age group, heart size, shunt group and right ventricular systolic pressure.

	R		rSR		rsr'		rS	
Age group	No.	%	No.	%	No.	%	No.	%
A	14	61	19	40	9	47	8	53
B	5	22	12	25	7	37	5	34
C	4	17	17	35	3	16	2	[illegible]
Total	[illegible]	100	48	100	19	100	15	100

	R		rSR		rsr		rS	
Heart size	No.	%	No.	%	No.	%	No.	%
Normal	3	14	6	13	4	1	4	27
Slight enlargement	16	73	25	54	8	42	8	53
Moderate enlargement	2	9	11	24	6	31	2	13
Pronounced enlargement	1	4	4	9	1	6	1	7
Total	22	100	46	100	19	100	15	100

	[illegible]		SR		rsr		rS	
Shunt group	No.	%	No.	%	No.	%	No.	%
1	4	18	6	13	4	21	3	20
2	11	50	17	37	8	42	8	53
3	7	32	23	50	7	37	4	27
Total	22	100	46	100	19	100	15	100

	R		SR		rsr'		S	
RV systolic pressure mm Hg	No.	%	N	%	No.	%	No.	%
50	8	36	20	43	7	38	6	40
> 50	14	64	26	57	12	62	9	60
Total	22	100	46	100	19	100	15	100

QRS complex

In spite of large variations in the QRS complex in lead V_1, it was possible in principle to classify the different types into the four QRS patterns shown in

R rSR rsr's' rS

Fig. 5 Configuration of QRS complex in lead V

TABLE [illegible] ECG patterns in lead V before and after operation

		Before operation				
		R	SR	rsr′	S	No. of patients
After operation	R	11	2	—	—	13
	SR	5	33	5	1	44
	rsr′s	1	9	[illegible]	—	16
	S	6	4	8	14	32
No. of patients		23	48	19	15	105

Fig 5 The preoperative QRS pattern in V_1 in relation to age group heart size shunt group and right ventricular systolic pressure can be seen in Table 8. For two patients no ECG recording in V_1 was made preoperatively

Preoperatively the R pattern was seen more frequently in the children (age group A) than in the adults (age groups B and C) while the rSR pattern was somewhat more frequent among the adults. Of the two other QRS patterns, the frequency was approximately equal in the children and adults.

All four types of complex showed the greatest frequency among patients with slight cardiac enlargement, and in addition the frequency of these types was greater in patients with normal heart size than in those with pronounced enlargement.

Further all types of QRS complex, except the rSR pattern, were seen most often in shunt group 2, while the rSR pattern was somewhat more frequent in shunt group 3

The rSR pattern was of approximately equal frequency in patients with normal as in those with raised systolic right ventricular pressures, while the other QRS patterns showed a greater frequency in patients in whom this pressure was raised.

Only in children was a significant correlation (*) seen between shunt size and the amplitude of the R wave in lead V_1 At the follow up examination no significant correlation was found, however between shunt reduction and reduction of the amplitude of the R wave, either in the children or the adults.

R pattern. This is consistent with right ventricular hypertrophy and the qR and rR complexes have also been included in this type. *Preoperatively* 23 patients showed this pattern in V_1 In 10 patients (4 children and 6 adults) a qR complex was seen.

Postoperatively the ECG pattern remained unchanged in 11 patients of this group which can be seen in Table 9

rSR pattern This complex, which is described as characteristic of atrial septal defect, is considered to be due to hypertrophy and/or dilatation of the right ventricular outflow tract rather than to right intraventricular conduction delay i.e. partial right bundle branch block (Pryor et al. 1959)

Preoperatively 48 patients showed this complex in V_1

Postoperatively this type of complex persisted in 33 patients (14 children and 19 adults) and, as seen in Table 9 2 of the patients now showed an R complex, 9 an rsr's complex and 4 a normal rS complex.

In the 33 patients in whom the QRS complex was unchanged, the amplitude of R was, on the average, 10.9 mm preoperatively and 7.0 mm, i e. significantly lower (***) postoperatively The reduction of the R amplitude was more pronounced in the children than in the adults.

The ventricular activation time (VAT) in V in these patients was 6.8 csec preoperatively and 6.3 csec, i.e. significantly shorter ( ) postoperatively

rsr pattern. This QRS complex, which differs from the more typical rSR pattern mainly by its generally lower amplitude and the terminal r' wave, is probably also, however an expression of right ventricular outflow tract hypertrophy this pattern was observed *preoperatively* in 19 patients.

The rsr s' pattern persisted *postoperatively* in 6 patients, while in 5 patients a more typical rSR complex, and in 8 patients a normal rS complex, were recorded.

S pattern. This pattern, which is normal in V was seen *preoperatively* in 15 patients.

Postoperatively the pattern remained unchanged in all except one patient.

Altogether 64 patients had the same type of QRS complex postoperatively as preoperatively of which 50 were abnormal 22 patients had different types of abnormal QRS pattern on the two occasions. In 18 patients newly acquired normal QRS complexes of the rS type were observed.

The amplitude of R in V_1 in those patients who did not exhibit the rSR pattern either pre- or postoperatively was, on the average, 6.9 mm preoperatively and 4 6 mm, i. e. significantly lower (***) postoperatively the decrease in R wave amplitude being most pronounced in patients with an R complex. On the other hand, no significant change was seen in VAT which in these 72 patients was, on the average, 3.9 csec preoperatively and 3.2 csec postoperatively

Preoperatively 70 patients showed a QRS complex of type Rs in *lead* V_6, and in 33 patients this complex was of the qRs type. The amplitude of the R wave in these complexes was, on the average, 14 4 mm.

Postoperatively 55 patients showed the Rs pattern, and 41 patients a pattern of the qRs type, with an average R wave amplitude of 18.1 mm, this being significantly higher (***) than preoperatively The QRS duration in lead V_6 was, on the average, 1 0 csec shorter postoperatively than preoperatively which was due to a significant (*) reduction of the duration of the S wave from an average of 4.2 to 3.3 csec.

QRS axis. Preoperatively the mean QRS axis in the frontal plane was 81 in the children, and 89° in the adults, and the corresponding postoperative values were 75 and 71° respectively

The *postoperative* change of the mean QRS axis towards the left was significant in the adults (***) and in the children ( )

TABLE 9 ECG patterns in lead V before and after operation

		Before operation				
		R	rSR	rsr	S	No. of patients
After operation	R	11	2	—	—	13
	rSR		33	5	1	44
	rsr	1	9	6	—	16
	rS	6	4	8	14	32
No of patients		3	48	19	15	105

Fig 5 The preoperative QRS pattern in V_1 in relation to age group heart size shunt group and right ventricular systolic pressure can be seen in Table 8. For two patients no ECG recording in V_1 was made preoperatively

Preoperatively the R pattern was seen more frequently in the children (age group A) than in the adults (age groups B and C) while the rSR pattern was somewhat more frequent among the adults. Of the two other QRS patterns, the frequency was approximately equal in the children and adults.

All four types of complex showed the greatest frequency among patients with slight cardiac enlargement, and in addition the frequency of these types was greater in patients with normal heart size than in those with pronounced enlargement.

Further all types of QRS complex, except the rSR pattern, were seen most often in shunt group 2 while the rSR pattern was somewhat more frequent in shunt group 3

The rSR pattern was of approximately equal frequency in patients with normal as in those with raised systolic right ventricular pressures, while the other QRS patterns showed a greater frequency in patients in whom this pressure was raised.

Only in children was a significant correlation (*) seen between shunt size and the amplitude of the R wave in lead V_1 At the follow up examination no significant correlation was found, however between shunt reduction and reduction of the amplitude of the R wave either in the children or the adults.

R pattern This is consistent with right ventricular hypertrophy and the qR and rR complexes have also been included in this type. *Preoperatively* 23 patients showed this pattern in V_1 In 10 patients (4 children and 6 adults) a qR complex was seen.

Postoperatively the ECG pattern remained unchanged in 11 patients of this group, which can be seen in Table 9

rSR pattern This complex, which is described as characteristic of atrial septal defect is considered to be due to hypertrophy and/or dilatation of the right ventricular outflow tract rather than to right intraventricular conduction delay i e. partial right bundle-branch block (Pryor et al. 1959)

Preoperatively 48 patients showed this complex in V_1

Postoperatively this type of complex persisted in 33 patients (14 children and 19 adults) and, as seen in Table 9 2 of the patients now showed an R complex, 9 an rsr's complex and 4 a normal rS complex.

In the 33 patients in whom the QRS complex was unchanged, the amplitude of R was, on the average, 10.9 mm preoperatively and 7.0 mm, i.e. significantly lower (***) postoperatively The reduction of the R amplitude was more pronounced in the children than in the adults.

The ventricular activation time (VAT) in V_1 in these patients was 6 8 csec preoperatively and 6.3 csec, i.e. significantly shorter ( ) postoperatively

rsr's pattern This QRS complex, which differs from the more typical rSR pattern *mainly by its generally lower* amplitude and the terminal s wave, is probably also, however an expression of right ventricular outflow tract hypertrophy this pattern was observed *preoperatively* in 19 patients.

The rsr's pattern persisted *postoperatively* in 6 patients, while in 5 patients a more typical rSR complex, and in 8 patients a normal rS complex, were recorded

S pattern This pattern, which is normal in V_1 was seen *preoperatively* in 15 patients

Postoperatively the pattern remained unchanged in all except one patient

Altogether 64 patients had the same type of QRS complex postoperatively as preoperatively of which 50 were abnormal 27 patients had different types of abnormal QRS pattern on the two occasions. In 18 patients newly acquired *normal QRS complexes of the rS type* were observed.

The amplitude of R in V_1 in those patients who did not exhibit the rSR pattern either pre- or postoperatively was, on the average, 6.9 mm preoperatively and 4.6 mm, i.e. significantly lower (***) postoperatively the decrease in R wave amplitude being most pronounced in patients with an R complex. *On the other hand, no significant change* was seen in VAT which in these 72 patients was, on the average, 3.9 csec preoperatively and 4 2 csec postoperatively

Preoperatively 70 patients showed a QRS complex of type Rs in *lead* V_6 and in 33 patients this complex was of the qRs type. The amplitude of the R wave in these complexes was, on the average, 14 4 mm

Postoperatively 55 *patients* showed the Rs pattern, and 41 patients a pattern of the qRs type, with an average R wave amplitude of 18.1 mm, this being significantly higher (***) than preoperatively The QRS duration in lead V was, on the average, 1 0 csec shorter postoperatively than preoperatively which was due to a significant ( ) reduction of the duration of the S wave from an average of 4.2 *to* 3.3 *csec.*

QRS axis. Preoperatively the mean QRS axis in the frontal plane was 81 in the children, and 89° in the adults, and the corresponding postoperative values were 5 and 71 respectively

The *postoperative* change of the mean QRS axis *towards the left* was significant in the adults (***) and in the children (*)

Preoperatively only 14 patients (5 children and 9 adults) had a definite right axis deviation (more than + 110°) and this remained unchanged after the operation in 6 patients. No definite left axis deviation was observed, but preoperatively 4 patients showed a mean QRS axis of between 0° and 30° and this was seen in 5 patients postoperatively In cases of complete right bundle branch block, only the first 7 csec of the QRS complex were used for calculation of the mean QRS axis.

QRS duration Preoperatively the QRS duration in lead II was 8.7 csec in the children and 9 4 csec in the adults.

Postoperatively there was no significant difference in the children (8.3 csec) but significant differences were noted in the adults (**) where the value was 8.5 csec.

The QRS duration was 10 csec or shorter in 92 patients preoperatively and in 96 patients postoperatively A QRS duration of 11 csec was observed in 7 patients preoperatively and in 5 patients postoperatively A complete right bundle branch block with a QRS duration of 12 csec or more was found preoperatively in 6 adult patients, in 4 of whom this persisted postoperatively

T waves

The most pronounced T wave change occurred in the *immediate postoperative period* On the day of operation the T wave amplitude was estimated in lead II in 49 patients and was, on the average 1 9 mm in 44 of these patients the S-T segment was considered normal, and in the remaining 5 somewhat elevated. On the first day after the operation a significant change was seen (***) the T wave amplitude now being 2.9 mm, on the average, and the S-T segment initially elevated in 74 out of 100 patients in lead II This pattern persisted on the second day but a gradual depression of S-T segment and the T wave was then seen up to the sixth day after the operation, by which time its amplitude was 0 8 mm and the S-T segment normal in 79 out of 92 patients.

During the first few weeks postoperatively a pronounced change in S-T and T was seen in the precordial leads, with depression of the S-T segment and flattening or inversion of the T wave. Two weeks, on the average, postoperatively 59 patients still showed a negative or pathologically low T wave in lead V_1, with an approximately equal incidence in the children and adults.

At the follow up examination the T wave amplitude in lead II was, on the average 2.6 mm thus showing no change from the preoperative value (2.4 mm) On the other hand, a pathologically low or negative T wave was observed in precordial leads V_1—V_4 in 42 patients (21 children and 21 adults) and in lead V_6 in 13 patients. Thirty of these 42 patients performed exercise tests postoperatively In half of them the T wave, which was inverted at rest, showed some normalization in the standing position during the orthostatic test and on deep inspiration. In all patients the T wave over the precordium gradually became normal with increasing work loads. This is an ECG reaction which may be seen in patients with previous

perimyocardial damage, and it has therefore been called "status post myocardial lesion" (Areskog and Hallén, 1964)

Discussion

The incidence of atrial fibrillation in ASD sec varies, but according to Wood (1962) who has discussed the haemodynamic effects and prognostic importance of atrial fibrillation in this condition, it is correlated particularly with age. Thus in the present series, of which only 4 patients were above 50 years of age, it was not surprising to find only one patient with atrial fibrillation — the oldest patient. In this patient the fibrillation was still resistant to therapy after the operation, and, together with pronounced cardiac enlargement, as seen roentgenologically it probably expressed an irreversible myocardial lesion.

In three patients with residual postoperative arrhythmia of the high-grade A-V block type, the long term prognosis is uncertain and in patients with uncomplicated ASD sec, a postoperative high grade A V block is a complication which may worsen the outlook considerably compared with the preoperative prognosis.

The postoperative arrhythmia in atrial septal defect is considered to be due to surgical trauma according to Popper et al. (1962) the manipulations especially in the vicinity of the A V node have an arrhythmia-inducing effect, and these authors state that apart from such factors the incidence of arrhythmia is only influenced by age

In the present series 57 patients (53 %) showed arrhythmia at some time during the first week postoperatively This is a rather higher figure than that of Popper et al. (1962) who found a total arrhythmia frequency of 43 % among a series of 126 secundum defects in their patients, however extracorporeal circulation was used, and from this aspect the two series are not entirely comparable. As in Popper series, in which the patients were, on the average, somewhat younger the incidence of arrhythmia in the present series increased with age.

The immediate postoperative supraventricular arrhythmia was, in most cases, of nodal origin. Since this arrhythmia was regular and of normal frequency it caused the patient no discomfort. This arrhythmia, which can be caused by temporary oedema in the atrio-ventricular nodal region (Gomez et al. 1962) ppeared to change to sinus rhythm spontaneously regardless of whether the patient received digitalis or not. Digitalis medication was not given as a routine preoperatively

Serious postoperative arrhythmias in ASD sec have been described by among others, Sellors (1961) and Derra et al. (1965) Derra et al. reported 2 cases of total A V block among a series of 700 surgically repaired secundum defects these two patients showed spontaneous regression within 2 months of the operation, however

Especially in the adults, postoperative arrhythmia often prolonged the period of hospitalization considerably and the increasing risk of arrythmia in ASD sec with advancing age, both with and without operation, indicates early surgery

The preoperative ECG changes in ASD sec have been discussed greatly especially as regards the correlation between ECG pattern and haemodynamics, and the aetiology of the typical rSR complex in lead V_1 Pryor Woodward and Blount (1959) in a study of 100 surgically closed secundum defects, found no applicable correlation between the QRS axis or height of R in lead V_1 and either the pulmonary arterial pressure, total pulmonary resistance or pulmonary flow A lack of correlation between ECG and haemodynamics has also been shown by Walker et al. (1955) and Barboza et al. (1958) *inter alia* but De Oliveira and Zimmerman (1958) and Lee and Scherlis (1962) on the other hand, found some correlation between the QRS pattern in lead V_1 and the magnitude of the left to-right shunt. In the present series, however a significant correlation (*) between shunt size and the amplitude of the R wave in lead V_1 was seen only in children. At the follow up examination no significant correlation was found between shunt reduction and reduction of the amplitude of the R wave, either in the children or the adults.

Cabrera and Monroy (1952) and Sodi Pallares and Marsico (1955) considered that incomplete right bundle-branch block (IRBBB) in atrial septal defect was due to diastolic overloading of the right ventricle, while on the contrary Walker et al. (1956) Blount et al. (1957) Silverblatt et al. (1957) and, in particular De Oliveira and Zimmerman (1958) did not regard IRBBB as representing conduction delay in the right branch, but rather the presence of anatomical right ventricular dilatation and/or selective hypertrophy of the right ventricular outflow tract (crista supraventricularis) resulting in delayed activation of this tract. Both groups of authors considered, however that right ventricular dilatation rather than right ventricular hypertrophy was typical in ASD patients with large left to-right shunts and essentially normal right ventricular pressures.

The preoperative ECG changes in this series agreed in the main with those described in uncomplicated ASD sec by Pryor et al. (1959) and Loogen et al. (1961) among others.

After closure of an atrial septal defect, the diastolic overloading of the right ventricle disappears. The dilatation of the right ventricle decreases, as also does the hypertrophy in the right ventricular outflow tract. As a result the amplitude of the R wave in lead V_1 is reduced, and the mean QRS axis changes towards the left (Davies et al 1960 Loogen et al. 1961) The regression of the preoperative ECG abnormalities is considered to indicate that the rSR pattern in lead V_1 is caused by dilatation and/or hypertrophy rather than intraventricular conduction delay since this can hardly be affected by the operation (De Oliveira and Zimmerman 1958 Davies et al. 1960) The P wave also decreases in both amplitude and duration after the operation (Sanchez-Cascos et al. 1963)

In the present series only six patients showed definite signs of atrial hypertrophy which seems a low figure in view of the previous finding of a frequency up to 30 % in ASD sec (Sánchez-Cascos et al. 1963) Only among the children were

significant (***) changes observed in the amplitude and duration of the P wave in lead II among the adults no change in amplitude was seen, but the duration was significantly (**) shorter. The postoperative decrease in the P wave must be an expression of flow reduction in the right atrium, even though no relationship was found preoperatively between shunt size and P wave pattern in lead II or V_1.

On comparing the pre- and postoperative QRS complexes, it was found that the QRS pattern in V was the same on both occasions in no fewer than 64 patients, and in 50 of the cases this pattern was considered to be pathological. Postoperatively a tendency towards normalization of the QRS pattern in V_1 was observed, but newly acquired normal QRS complexes of the rS type with an R/S ratio of less than 1 were seen in only 18 patients. Thus even though in most cases the *type* of QRS pattern remained unchanged, the *degree* of abnormality had decreased, especially as regards the amplitude of R or R' in lead V. In the 33 patients with the same characteristic secundum complex of the rSR' type in V pre- and postoperatively the activation time was only almost significantly shorter ( ) postoperatively than preoperatively while the amplitude was highly significantly lower (***). This may indicate that in these cases the amplitude reduction corresponded to regression of the hypertrophy and/or dilatation in the right ventricular outflow tract while, on the other hand, a residual QRS pattern with a split complex may point to a congenital abnormality in the right bundle branch. Thus also corresponds to changes over the left ventricle (lead V_6) where a more pronounced *increase* (***) of the R wave amplitude was seen, as a sign of increased left ventricular activity while, on the other hand, the reduction of the preoperatively wide S wave, probably caused by right ventricular conduction delay was less pronounced (*).

A postoperative pathological QRS complex in V_1 differing more in degree than in type from the *preoperative* pattern was not thus an expression of a residual shunt, even though in some isolated cases the reduction in amplitude of the R wave was not especially pronounced.

Elevation of the S-T segment and inversion of the T wave in the immediate postoperative period are usually seen after open heart surgery (Areskog and Hallén, 1964). The S-T segment becomes normal after about a week, while the T wave change in the precordial leads may persist for a very long time. In the present series, at the follow-up examination pathological T wave changes were recorded in precordial leads V_1—V in 42 patients and in lead V_6 in 13 patients. These T wave abnormalities, probably caused by perimyocardial disturbances during the operation, were of the "status post myocardial lesion" type, and gradually became normal during exercise tests. Similar types of ECG reactions with normalization of negative T waves during and after exercise have been described in myocardial lesions caused by *infarction* (Stokes 1946, Söderholm et al. 1962, Areskog and Hallén 1964) and in cardiomyopathy in Friedreich's ataxia (Thorén 1964).

and occur after open heart surgery not only in ASD sec but also in other cases. In approximately half of the patients in the present series some normalization of the T wave was observed on deep inspiration. A similar ECG response in healthy persons has been described by Blackman and Kuskin (1964) who considered that such a change in the T wave could be explained by the change in position of the heart during deep inspiration. In a number of cases where the part of the left lung covering the anterior region of the heart (the "cardiac notch") was poorly ventilated, Blackman and Kuskin recorded T waves, in leads V_3—V_4 of the type also seen in direct epicardial recording. On deep inspiration the distance between the heart and the thoracic wall is increased by the air filled lung which is a poor conductor of electrical currents, and the T wave amplitude changes.

In cases of surgically repaired ASD sec there is no definite reason to assume that the normalization of the T wave during exercise is due to changes in the myocardial metabolism or improved coronary perfusion resulting from vasodilatation as has been discussed in connection with S-T and T alteration during exercise after myocardial infarcts. Hyperactivity of the sympathetic nervous system may explain depression and/or inversion of the T wave which changes can be normalized by the use of ganglia blocking media (Linderholm et al. 1962, Thorén 1964). This was not tested in the present series. After a thoracotomy the occurrence of small pleural adhesions can probably be assumed which could make air filling of the "cardiac notch" difficult, and contribute to the occurrence of T wave changes especially in those cases where some normalization of the T wave on deep inspiration has been observed. These postoperative T wave abnormalities, which may thus be caused by a vegetative or functional mechanism are considered to be benign in character and are not to be regarded as unfavourable.

Summary

ECG studies were made on 107 patients with ASD sec before and after operation. Preoperatively one patient showed atrial fibrillation. Postoperative arrhythmia occurred in 57 patients but 8 days after the operation this was observed in only 21 patients. A tendency to immediate postoperative arrythmia was seen especially in patients with large, low ASD sec. Five patients showed arrhythmia at the follow up examination, but only 3 patients at a later examination two of these three patients had an A V block II and the third an A V block III the latter requiring pacemaker therapy.

No relationship was found between shunt magnitude and the duration of amplitude of the P wave. Only 6 patients showed preoperative signs of atrial hypertrophy.

The preoperative ECG findings in this series were of the type usually described in ASD sec. In lead V_1 four principal types of QRS complex were distinguished. 50 patients showed the same pathological QRS complex postoperatively as preoperatively thus being of the "ASD sec" type, with an rSR pattern, in 33 of these patients. The QRS

complex was evaluated as normal in 15 patients preoperatively and 3? patients postoperatively. In this series a significant correlation ( ) between shunt size and the amplitude of the R wave in lead V was seen only in children. At the follow-up examination, however no significant correlation was found between shunt reduction and reduction of the amplitude of the R wave, either in the children or the adults.

Preoperatively only 14 patients showed a definite right axis deviation (more than + 110°). No definite left axis deviation (less than —30°) was seen. The postoperative change of the mean QRS axis towards the left was more marked in the adults than in the children.

Postoperatively the QRS duration was shorter in the adults but, on the average, unchanged in the children. Complete right bundle branch block with a QRS duration of 12 csec or more occurred preoperatively in [illegible] adult patients.

During the immediate postoperative period the S-T segment and T wave showed changes of the type usually seen in pericarditis. At the follow-up examination there was a residual pathological T wave in lead V_4 in 42 patients. In 30 patients who performed work tests, normalization of the T wave, which at rest was inversed, was observed during and after exercise. The reason for this "status post myocardial lesion" reaction is discussed and is considered to be of no functional importance. This pathological T wave at rest though observed for a long period after the operation, should not thus be regarded as unfavourable.

and occur after open heart surgery not only in ASD sec but also in other cases. In approximately half of the patients in the present series some normalization of the T wave was observed on deep inspiration. A similar ECG response in healthy persons has been described by *Blackman and Kuskin (1964)* who considered that such a change in the T wave could be explained by the change in position of the heart during deep inspiration. In a number of cases where the part of the left lung covering the anterior region of the heart (the "cardiac notch") was poorly ventilated Blackman and Kuskin recorded T waves in leads V_2—V_4 of the type also seen in direct epicardial recording. On deep inspiration the distance between the heart and the thoracic wall is increased by the air filled lung which is a poor conductor of electrical currents, and the T wave amplitude changes.

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Comparisons were made between the results obtained on catheterization before operation and at the follow-up examination in the entire series of 107 patients, with respect to oxygen saturation and pressure at rest. The magnitude of the left-to-right shunt, expressed approximately as per cent of the pulmonary blood flow was evaluated in relation to age, systolic right ventricular pressure and relative heart volume.

The results obtained on cardiac catheterization at rest before operation and at the follow-up examination are

PA				PCV		LA		LV			Left to right shunt per cent of pulm. blood flow	
No.	S	D	M	No.	M	No.	M	No.	S	D	No.	
30	26	10	17	26	7.2	26	5.1	17	[illegible]	4.7	31	56
19	25	9	16	17	7.4	16	5.6	11	[illegible]	5.2	19	65
49	25	9	17	43	7.3	42	5.5	28	[illegible]	4.9	50	59
	11	5	8		5		1		80	0		30
	50	24	40		12		11		150	9		86
[illegible]	25	9	15	18	6.5	16	5.9	7	101	3.9	22	62
7	25	8	14	3	6.2	5	4.0	2	105	2.0	7	54
29	25	9	15	23	6.4	21	5.4	9	102	4.9	29	60
	16	4	8		1		1		85	0		37
	50	[illegible]	30		12		9		130	6		81
21	28	10	17	17	4.5	10	4.5	8	117	5.9	20	65
6	31	9	15	5	6.2	3	3.7	2	112	5.5	6	64
27	29	10	16	22	4.8	13	4.3	10	117	5.8	26	65
	14	4	7		1		1		105	1		33
	80	25	40		8		[illegible]		140	10		87
73	26	9	16	61	6.2	52	5.3	52	103	5.3	73	60
[illegible]	26	9	15	27	7.0	24	5.0	15	101	4.7	52	62
105	26	9	16	88	6.4	76	5.2	47	103	5.1	105	61
	11	4	7		1		1		80	[illegible]		30
	80	25	40		12		11		150	10		87
	9.0	3.3	4.9		2.5		2.3		18.7	3.5		14.6
	0.9	0.3	0.5		0.3		0.3		2.8	0.3		2.4

PCV = pulmonary capillary venous pressure
LA = left atrium
LV = left ventricle
S = systolic pressure
D = diastolic pressure
M = mean pressure

Haemodynamic findings at rest before and after operation in 107 patients

TABLE 10 Preoperative observations during heart catheterization at rest in 107 cases with ASD sec.

Age groups and sex	Characteristic	Oxygen saturation per cent						Pressures, mm Hg				
								RA		RV		
		No.	LA	No.	PA	No.	SVC	No.	M	No.	S	D
A Girls	mean	25	96	[illegible]	83	31	67	31	4 0	31	33	2.5
Boys	»	16	96	19	87	19	66	19	4 4	19	29	3.2
Total	»	41	96	50	84	50	67	50	4 1	50	31	2.7
	min		91		68		50		1		16	0
	max.		100		93		78		10		46	8
B Women	mean	15	97	21	85	22	63	21	4 0	22	[illegible]	3 4
Men	»	5	98	6	84	7	69	7	3.4	7	32	1 4
Total	»	20	97	27	85	[illegible]	65	28	3.9	29	[illegible]	2.9
	min.		97		80		55		—0.5		20	0
	max.		100		90		75		8		64	9
C Women	mean	8	95	20	85	18	64	21	2.5	21	33	3.2
Men	»	2	97	6	84	[illegible]	63	6	3.3	5	33	2.0
Total	»	10	95	26	85	24	63	27	2 7	26	33	3 0
	min.		90		78		56		—1		22	0
	max.		99		91		81		8		87	7
A+B+C												
Women	mean	48	96	72	84	71	65	73	3 6	74	33	3.0
Men	»	23	96	[illegible]	85	32	66	32	4 0	31	31	2.6
Total	»	71	96	103	84	103	65	105	3 7	105	32	2.8
	min		90		68		50		—1		16	0
	max.		100		93		81		10		87	9
	SD		2 4		4.2		5.9		6.2		10 1	2.5
	SE		0 3		0.4		0.6		0.6		1.0	0.2

Age group A: Children up to 15 years.
B Women and men 15—29 years
C: Women and men 30 years or more

SVC = superior vena cava
RA = right atrium
RV = right ventricle
PA = pulmonary artery

Comparisons were made between the results obtained on catheterization before operation and at the follow-up examination in the entire series of 107 patients, with respect to oxygen saturation and *pressure at rest. The magnitude of the* left-to-right shunt, expressed approximately as per cent of the pulmonary blood flow was evaluated *in relation to* age, systolic right ventricular pressure and relative heart volume.

The results obtained on cardiac *catheterization at rest* before operation and at *the follow-up examination* are

PA				PCV		LA		LV			Left to right shunt per cent of pulm. blood flow	
No.	S	D	M	No.	M	No.	M	No.	S	D	No	
30	26	10	17	26	7.2	26	5.1	17	97	4.7	31	56
19	25	9	16	17	7.4	16	5.6	11	98	5.2	19	63
49	25	9	17	43	7.3	42	5.3	28	98	4.9	50	58
	11	5	[illegible]		3		1		[illegible]	0		30
	50	24	40		12		11		130	9		86
22	25	9	15	18	6.5	16	5.9	7	101	5.9	[illegible]	[illegible]
7	23	[illegible]	14	5	6.2	5	4.0	2	105	2.0	7	54
29	23	[illegible]	15	[illegible]	6.4	21	5.4	9	102	4.9	[illegible]	60
	16	4	8		1		1		85	0		37
	30	25	30		12		9		130	[illegible]		81
21	28	10	17	17	4.5	10	4.5	8	117	5.9	20	65
6	[illegible]	9	15	5	8.2	3	3.7	2	112	5.5	6	64
27	29	10	16	22	4.8	13	4.3	10	117	5.8	26	[illegible]
	14	4	7		1		1		105	1		33
	80	[illegible]	40		8		10		140	10		87
73	26	[illegible]	16	61	6.2	52	5.3	32	103	5.3	73	60
32	28	9	1	27	7.0	24	5.0	15	101	4.7	32	62
105	26	9	16	88	6.4	76	5.2	47	103	5.1	105	61
	11	4	7		1		1		80	[illegible]		30
	80	23	40		12		11		130	10		87
	9.0	3.3	4.9		2.3		2.3		18.7	3.5		14.6
	0.9	0.3	0.5		0.3		0.3		2.8	0.3		1.4

PCV — pulmonary capillary venous pressure
LA — left atrium
LV — left ventricle
S — systolic pressure
D — diastolic pressure
M — mean pressure

TABLE 11 Postoperative observations during heart catheterization at rest in 107 cases with ASD sec.

Age groups and sex	Characteristic	Oxygen saturation per cent				Pressures, mm Hg	
						RA	
		No.	PA	No.	SVC	No.	M
A Girls	mean	30	70	31	69	31	2.7
Boys	»	19	71	19	69	19	2.7
Total	»	49	70	50	69	50	2.7
	min.		60		60		[illegible]
	max.		78		79		7
B Women	mean	18	72	17	69	22	1 7
Men	»	6	72	6	73	7	1.0
Total	»	24	72	23	70	29	1.5
	min.		64		60		—2
	max.		77		78		6
C Women	mean	21	69	20	68	22	1 4
Men	»	6	[illegible]	6	68	6	1.6
Total	»	27	69	26	68	28	1.5
	min.		58		53		—1
	max.		77		75		6
A+B+C							
Women	mean	69	70	68	69	75	2.0
Men	»	31	71	31	70	3	2 1
Total	»	100	0	99	69	107	2.0
	min.		58		53		—2
	max.		78		79		7
	SD		4.2		4.5		2.0
	SE		0 4		0 4		0.2

summarized in Tables 10 and 11 and Figures 6—8 Some individual values, either preoperative or for the follow up examination were not obtainable, and for this reason the number of values sometimes varies in the different tables and figures.

Oxygen saturation

Left atrium In 71 patients the oxygen saturation in the left atrium was recorded, the value obtained being, on the average, 96 % In 3 patients the value was below normal 2 patients with a value of 90 % were found on operation to have large low defects with prerequisite conditions for a right to-left shunt. These patients had no pulmonary hypertension nor cyanosis. In the third patient the oxygen saturation was 90 % in the left atrium, brachial artery and pulmonary vein This patient also showed moderately pronounced pulmonary hypertension.

Superior vena cava (Fig 6) *Preoperatively* the oxygen saturation in the superior vena cava was, on the average 65 % In 18 patients with anomalous

Abbreviations as in Table 10.

RV			PA				PCV	
No.	S	D	No.	S	D	M	No.	M
31	24	2.4	31	22	8	14	23	7.2
19	24	2.4	19	23	10	15	18	7.7
50	24	2.4	50	22	9	15	41	7.4
	13	[illegible]		12	3	10		2
	37	9		37	16	26		13
[illegible]	23	1.6	22	21	7	12	22	5.7
7	[illegible]	1.7	7	17	7	10	7	5.5
29	22	1.6	29	20	7	11	29	5.6
	10	—4		10	2	7		1
	50	6		40	15	27		12
20	24	3.1	20	24	9	13	18	5.6
[illegible]	[illegible]	2.3	3	23	7	12	4	4.0
28	[illegible]	2.9	2.	24	[illegible]	13	22	5.3
	18	0		14	3	[illegible]		[illegible]
	45	8		35	18	22		12
73	24	4	[illegible]	22	8	13	63	6.4
32	23	2.3	31	21	8	13	29	6.6
105	24	2.3	104	22	8	13	92	[illegible]
	10	—4		[illegible]	2	7		0
	50	9		40	16	27		13
	6.4	2.3		6.2	3.2	4.3		3.2
	0.6	0.2		0.6	0.5	0.4		0.3

enous return to the superior vena cava, the saturation values were obtained above the entrance of the pulmonary veins, and these were found to be within the normal range in all cases except one.

At recatheterization the oxygen saturation in the superior vena cava was, on the average, 69 %; this was significantly (***) higher than before the operation.

Pulmonary artery (Fig. 7). *Preoperatively* the oxygen saturation in the pulmonary artery was, on the average, 84 % and varied between 80 % and 90 % in 82 patients. In 7 patients with a very high left-to-right shunt this value was 90 % or more. In 8 patients the oxygen saturation was lower than 80 %. In two girls with particularly low values (72 % and 68 %) the left-to-right shunt was estimated to be about 30 %. The difference in oxygen saturation between the pulmonary artery and superior vena cava in the entire series was, on the average, 19 %.

On *recatheterization* the oxygen saturation in the pulmonary artery was, on

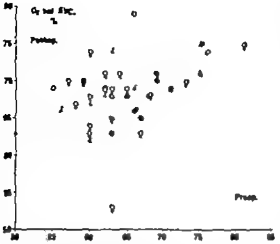

Fig 6. Oxygen saturation in in superior vena cava (SVC) on catheterization before operation (preop) and t follow-up examination (post p.) Circles represent women, triangles men open symbols = age group A, filled symbols = age group B. Circles with crosses, and triangles w th arrows represent patients in age group C. Age group A = children age group B = patients 15—29 y ars age group C = patients 30 years or older

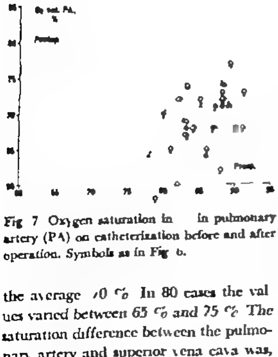

Fig 7 Oxygen saturation in in pulmonary artery (PA) on catheterization before and after operation. Symbols as in Fig 6.

the average 70 % In 80 cases the values varied between 65 % and 75 % The saturation difference between the pulmonary artery and superior vena cava was, on the average, 1 % No signs of a residual left to-right shunt were observed in any of the 107 patients. In 5 patients with a somewhat high oxygen saturation (77—78 %) however the saturation difference between the pulmonary artery and superior vena cava was only 3 %. In 8 patients rather low values of between 58 % and 64 % were noted.

Left to-right shunt, heart volume and systolic right ventricular pressure

Preoperatively the *left-to-right shunt* was, on the average 61 % of the pulmonary blood flow in two patients this value was unobtainable. No residual shunts were found at the follow-up examination. The distributions of patients in the different shunt and X ray groups according to age groups is seen in Table 12. Eighteen patients (10 children and 8 adults) belonged to shunt group 1 The frequency of children (age group A) in shunt groups 2 and 3 was approximately equal, while the young adults (age group B) showed a greater frequency in shunt group 2 and the older adults (age group C) in shunt group 3.

A normal *heart volume* was seen in a total of 19 patients, 10 of whom were young adults in shunt group 2. Slight heart enlargement was observed in just over half i e. 58 of the patients, with a somewhat greater frequency in the children than in the adults. Moderate or pronounced heart enlargement was seen in 28 patients with predominance among the children, and older adults of shunt group 3

The *systolic right ventricular pressure* was 30 mm Hg or more in 61 out of 107 patients In only 6 patients was this 50 mm Hg or more As seen in Table 13 normal systolic right ventricular pres-

TABLE 12. Distribution of patients in the different shunt and X-ray groups according to age groups.

Age group A

Heart size	Shunt group			Total	
	1	2	3	No.	%
Normal	4	1	—	5	10
Slight enlargement	4	17	[illegible]	33	66
Moderate enlargement	2	4	4	10	20
Pronounced enlargement	—	—	2	2	4
Total No.	10	22	18	50	
Total %	20	44	36		100

Age group B

Heart size	Shunt group			Total	
	1	2	3	No.	%
Normal	1	10	2	12	41
Slight enlargement	4	5	4	13	45
Moderate enlargement	—	1	2	3	11
Pronounced enlargement	—	1	—	1	3
Total No.	4	17	8	29	
Total %	14	58	28		100

Age group C

Heart size	Shunt group			Total	
	1	2	3	No.	%
Normal	1	1	—	2	7
Slight enlargement	2	3	7	12	47
Moderate enlargement	1	1	6	8	31
Pronounced enlargement	—	2	2	4	15
Total No.	4	7	15	26	
Total	16	27	57		100

sures were more frequent in children than in adults, and in shunt groups 1 and normal values for this pressure were just as frequent as raised values. In shunt group 3, on the other hand, raised systolic right ventricular pressures were most frequent, especially among the older adults. In many cases there was some relationship between size of left-to-right shunt and heart volume.

In the present series, however, no significant correlation was found between

Table 13 Distribution of patients in shunt and age groups according to RV systolic pressure.

Shunt group	RV systolic pressure, mm Hg	Age group A	B	C	Total
1	< 30	5	1	2	8
	> 30	5	3	1	9
2	< 30	13	7	3	23
	> 30	9	10	2	1
3	< 30	7	2	1	10
	> 30	11	6	14	31

the size of the left to-right shunt, expressed in % of the pulmonary blood flow and the preoperative roentgenological heart volume, expressed in ml/m² body surface area in any of the age groups. In the older adults, however there was a significant correlation (*) between shunt size and systolic right ventricular pressure but this was not found in the other two age groups.

At the follow up examination no statistically certain correlation was found between shunt reduction and reduction of the relative heart volume or systolic right ventricular pressure, in the different age groups.

Intracardiac and intravascular pressures

The pressure results obtained on cardiac catheterization at rest before and after operation are summarized in Fig 8

Right atrium (RA) Preoperatively the mean pressure in the right atrium was, on the average 3 7 mm Hg In 24 patients, including 12 children a mean pressure of over 5 mm Hg was found.

At *recatheterization* the mean pressure was 2.0 mm Hg In 72 patients the pressure was lower than before the operation in 17 patients it was unchanged and in 16 patients somewhat higher 6 patients showed a mean pressure of more than 5 mm Hg The mean pressure in RA, both preoperatively and at recatheterization, was somewhat higher in the children than in the older adults. This pressure was significantly (**) lower postoperatively than preoperatively

Right ventricle (RV) Preoperatively the systolic pressure in the right ventricle was moderately raised 32 mm Hg [illegible] patients showed a pressure of 30 mm Hg or higher this being somewhat more frequent in adults than in children. In 6 patients this pressure was 50 mm Hg or higher Three of these had mild valvular pulmonary stenosis, which in two cases necessitated valvulotomy at the operation. In the third patient the systolic right ventricular pressure was still 50 mm Hg on recatheterization.

The end-diastolic pressure was, on the average, 2 8 mm Hg i e. normal and the diastolic pressure gradient between the right atrium and right ventricle was 0.9 mm Hg

On *recatheterization* the systolic right ventricular pressure was normal 24 mm Hg In 87 patients this pressure was now lower than preoperatively In one patient it was unchanged and in 16 patients somewhat higher In 16 patients (8 children 5 young adults and 3 older adults) the pressure remained at 30 mm Hg or higher

The end-diastolic pressure was essentially unchanged, 2.3 mm Hg

The systolic right ventricular pressure was significantly lower (***) on re

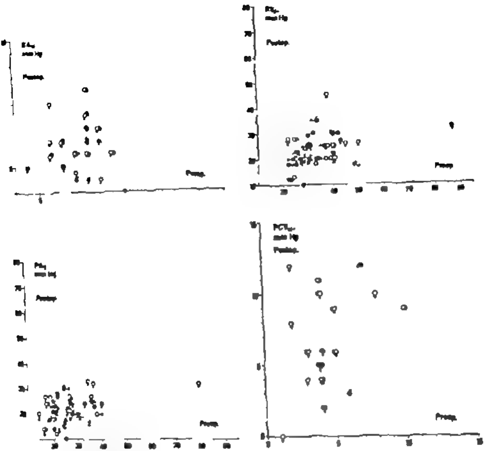

Fig. 8. Mean right atrial (RA) and pulmonary capillary venous (PCV) pressures, and systolic pressure in right ventricle (RV) and pulmonary artery (PA) in mm Hg before and after operation. Symbols as in Fig. 6.

catheterization than preoperatively. Neither before operation nor at recatheterization was there any definite sex or age difference with regard to the systolic or diastolic right ventricular pressures.

Pulmonary artery (PA). Preoperatively the systolic pressure in the pulmonary artery was, on the average, 26 mm Hg. In 27 patients this pressure was 30 mm Hg or higher, this value being somewhat more frequent in adults than in children. Only 3 patients had pulmonary hypertension, with systolic PA pressure of 50 mm Hg or more. In 2 of these patients this pressure was 50 mm Hg, and in 1 patient 80 mm Hg.

The diastolic and mean pressures were normal, with average values of 9 mm and 16 mm Hg, respectively.

The systolic *pressure gradient* between RV and PA was, on the average, 7 mm Hg. No definite relationship was found

TABLE 13 Distribution of patients in shunt and age groups according to RV systolic pressure.

Shunt group	RV systolic pressure, mm Hg	Age group A	B	C	Total
1	< 30	5	1	2	8
	> 30	5	3	1	9
2	< 30	13	7	3	23
	> 30	9	10	2	21
3	< 30	7	2	1	10
	> 30	11	6	14	31

the size of the left-to-right shunt expressed in % of the pulmonary blood flow and the preoperative roentgenological heart volume, expressed in ml/m² body surface area, in any of the age groups. In the older adults, however there was a significant correlation (*) between shunt size and systolic right ventricular pressure, but this was not found in the other two age groups.

At the follow-up examination no statistically certain correlation was found between shunt reduction and reduction of the relative heart volume or systolic right ventricular pressure, in the different age groups.

Intracardiac and intravascular pressures

The pressure results obtained on cardiac catheterization at rest before and after operation are summarized in Fig 8.

Right atrium (RA) *Preoperatively* the mean pressure in the right atrium was on the average, 3 7 mm Hg In 24 patients, including 12 children, a mean pressure of over 5 mm Hg was found.

At *recatheterization* the mean pressure was 2.0 mm Hg In 72 patients the pressure was lower than before the operation in 17 patients it was unchanged and in 16 patients somewhat higher 6 patients showed a mean pressure of more than 5 mm Hg The mean pressure in RA, both preoperatively and at recatheterization, was somewhat higher in the children than in the older adults. This pressure was significantly (**) lower postoperatively than preoperatively

Right ventricle (RV) Preoperatively the systolic pressure in the right ventricle was moderately raised, 32 mm Hg 63 patients showed a pressure of 30 mm Hg or higher this being somewhat more *frequent in adults than in children.* In 6 patients this pressure was 50 mm Hg or higher Three of these had mild valvular pulmonary stenosis, which in two cases necessitated valvulotomy at the operation. In the third patient the systolic right ventricular pressure was still 50 mm Hg on recatheterization.

The end-diastolic pressure was, on the average, 2 8 mm Hg, i.e. normal, and the diastolic pressure gradient between the right atrium and right ventricle was 0.9 mm Hg

On *recatheterization* the systolic right ventricular pressure was normal, 24 mm Hg In 87 patients this pressure was now lower than preoperatively In one patient it was unchanged and in 16 patients somewhat higher In 16 patients (8 children, 5 young adults and 3 older adults) the pressure remained at 30 mm Hg or higher

The end-diastolic pressure was essentially unchanged, 2.3 mm Hg

The systolic right ventricular pressure was significantly lower (***) on re-

pect completely normal conditions of pressure and oxygen saturation. If, on recatheterization, pathological changes are found, these may be attributable either to a residual left-to-right shunt, i.e. incomplete closure of the defect, or to incomplete regression of preoperative pathological conditions: this latter in turn may be due either to the fact that these conditions are not reversible, or may indicate a too short observation period after operation. In the present series no residual shunts were found, and the observation period between operation and follow-up examination was sufficiently long to allow a return to normal haemodynamic conditions.

It is always difficult to compare different clinical series. On evaluation of the present preoperative clinical and haemodynamic data certain differences were found from the results in atrial septal defect reported previously by Jonsson et al. (1957), Kjellberg et al. (1959), Davidsen (1960), Bedford (1961), Reindell et al. (1962), Storstein and Efskind (1963), and others: this can probably be explained by differences in the composition of the material with respect to age, types of defect and complicating abnormalities. With only few exceptions, the present series consisted by chance of patients with haemodynamically uncomplicated atrial septal defects of the secundum type and can probably be regarded as representative of patients with this disease up to the age of 60 years.

When cyanosis occurs in atrial septal defect of the secundum type, the reason is usually suspected to be a right-to-left shunt caused by increase in resistance in the pulmonary circulation (Besterman 1961), in which case closure of the defect is contraindicated.

Woolf (1963) found, however, that raised pressure in the pulmonary artery in patients with ASD could give rise to oedema in the alveolar-capillary membrane and reduced arterial oxygen saturation. This could probably explain the slight cyanosis noted preoperatively in one patient with moderately pronounced pulmonary hypertension of the hyperkinetic type and with reduced oxygen saturation in the pulmonary veins. After operation, performed with the aid of extracorporeal circulation, normalization of the pressures was observed, and normal saturation values, which indicates that a reversible change of the above type may have taken place. It is evident from the case described here that other causes for cyanosis in ASD sec. can sometimes be demonstrated, which may mean that the patient can undergo operation with a good result.

Kjellberg et al. (1959) found that low posteriorly situated secundum defects, with the opening of the inferior vena cava directed towards the left atrium, could give rise to insignificant right-to-left shunts with reduced oxygen saturation in the left atrium, even though the pressure there was higher than in the right atrium. This was probably the explanation for the reduced oxygen saturation in the left atrium in two children with a normal pulmonary venous saturation, in whom maximal low posteriorly situated defects were found at operation.

It was of interest to note in the present series that the oxygen saturation in the superior vena cava lay at a normal level

between magnitude of shunt and pressure gradient. The pressure gradient is assessed from withdrawal curves, except in 8 patients with a technically negative gradient. In 64 out of 103 patients the systolic gradient between RV and PA was less than 10 mm Hg in 25 patients this gradient lay between 10 and 20 mm Hg and in only 6 patients was it above 20 mm Hg In three patients with gradients of 31 36, and 40 mm Hg, mild pulmonary valvular stenosis was present.

At *recatheterization* the systolic PA pressure was, on the average, 22 mm Hg In 68 patients this pressure was now lower in 3 patients it was unchanged and in 31 patients somewhat higher in 14 of these latter patients a value of 30 mm Hg or more was noted The systolic pressure in the pulmonary artery was, on the average, almost significantly (*) lower postoperatively than before operation.

The diastolic and mean pressures were 8 mm and 13 mm Hg, respectively

The systolic *pressure gradient* between RV and PA was now on the average, 2 mm Hg In 77 patients the gradient was lower than before the operation in 5 it was unchanged and in 16 patients somewhat higher This gradient was significantly (**) lower on recatheterization than preoperatively

Pulmonary capillary venous (PCV) pressure Preoperatively the mean PCV pressure was normal being on the average 8 4 mm Hg The mean pressure was somewhat lower in older than in young patients.

On *recatheterization* this mean pressure was found on the average to be unchanged 6.5 mm Hg In 37 patients, however the value was higher than preoperatively while in 8 it was unchanged and in 29 lower The mean pressure was also now on the average, somewhat lower in older and young adults than in children

There was no statistically significant change in the mean PCV pressure after the operation.

Left atrium (LA) Preoperatively the mean pressure in the left atrium was recorded in 76 patients and was found, on the average, to be 5 2 mm Hg, and somewhat higher in children and young adults than in the older persons. The difference in mean pressure between left and right atrium was, on the average 1.5 mm Hg and the corresponding value for PCV and left atrium 1 2 mm Hg The difference in mean pressure between PCV and right atrium was 2.7 mm Hg before the operation and 4.5 mm Hg at the follow up examination.

Left ventricle (LV) Preoperatively the left ventricular pressure was recorded in 47 patients this was found to be, on the average, 98 mm Hg in children, 102 mm Hg in young adults and 117 mm Hg in the older adults. The end-diastolic pressures in these three age groups were 4 9 4 9 and 5 8 mm Hg respectively There was no end-diastolic pressure difference between left atrium and left ventricle. The difference in end-diastolic pressure between the left and right ventricles was, on the average 2 3 mm Hg

Discussion

After successful surgical repair of an uncomplicated atrial septal defect of the secundum type there is reason to ex

pect completely normal conditions of pressure and oxygen saturation. If on recatheterization, pathological changes are found, these may be attributable either to a residual left-to-right shunt, i.e. incomplete closure of the defect, or to incomplete regression of preoperative pathological conditions: this latter in turn may be due either to the fact that these conditions are not reversible, or may indicate a too short observation period after operation. In the present *series no residual shunts were found*, and the observation period between operation and follow-up examination was sufficiently long to allow a return to normal haemodynamic conditions.

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between magnitude of shunt and pressure gradient. The pressure gradient is assessed from withdrawal curves, except in 8 patients with a technically negative gradient. In 64 out of 103 patients the systolic gradient between RV and PA was less than 10 mm Hg, in 25 patients this gradient lay between 10 and 20 mm Hg, and in only 6 patients was it above 20 mm Hg. In three patients with gradients of 31, 36 and 40 mm Hg mild pulmonary valvular stenosis was present.

At *recatheterization* the systolic PA pressure was, on the average 22 mm Hg. In 68 patients this pressure was now lower, in 3 patients it was unchanged and in 31 patients somewhat higher; in 14 of these latter patients a value of 30 mm Hg or more was noted. The systolic pressure in the pulmonary artery was, on the average, almost significantly (*) lower postoperatively than before operation.

The diastolic and mean pressures were 8 mm and 13 mm Hg, respectively.

The systolic *pressure gradient* between RV and PA was now, on the average 2 mm Hg. In 77 patients the gradient was lower than before the operation, in 5 it was unchanged and in 16 patients somewhat higher. This gradient was significantly (**) lower on recatheterization than preoperatively.

Pulmonary capillary venous (PCV) pressure. Preoperatively the mean PCV pressure was normal, being on the average 6.4 mm Hg. The mean pressure was somewhat lower in older than in young patients.

On *recatheterization* this mean pressure was found, on the average, to be unchanged, 6.5 mm Hg. In 37 patients however the value was higher than preoperatively, while in 8 it was unchanged and in 29 lower. The mean pressure was also now, on the average, somewhat lower in older and young adults than in children.

There was no statistically significant change in the mean PCV pressure after the operation.

Left atrium (LA). Preoperatively the mean pressure in the left atrium was recorded in 76 patients and was found, on the average, to be 5.2 mm Hg and somewhat higher in children and young adults than in the older persons. The difference in mean pressure between left and right atrium was, on the average, 1.5 mm Hg, and the corresponding value for PCV and left atrium 1.2 mm Hg. The difference in mean pressure between PCV and right atrium was 2.7 mm Hg before the operation and 4.5 mm Hg at the follow up examination.

Left ventricle (LV). Preoperatively the left ventricular pressure was recorded in 47 patients; this was found to be, on the average, 98 mm Hg in children, 102 mm Hg in young adults and 117 mm Hg in the older adults. The end-diastolic pressures in these three age groups were 4.9, 4.9 and 5.8 mm Hg, respectively. There was no end-diastolic pressure difference between left atrium and left ventricle. The difference in end-diastolic pressure between the left and right ventricles was, on the average, 2.3 mm Hg.

Discussion

After successful surgical repair of an uncomplicated atrial septal defect of the secundum type, there is reason to ex

higher in the young than in the older adults, which is in agreement with investigations in normal persons according to Granath et al. (1964). It is always difficult in clinical series to assess the significance of small pressure differences, especially where mean pressures and filling pressures are concerned. The mean PCV pressure was, however, the only pressure which showed no significant change, this remaining at a normal level at the follow-up examination. Preoperatively the mean PCV pressure was, on the average, 1 mm higher than the mean pressure in the left atrium, and therefore this pressure difference was probably of approximately equal magnitude postoperatively also. In that case the postoperative pressure difference between the atria will be normal, i.e. approximately 3 mm Hg, which then means normal filling pressures in the respective ventricles. This also means that preoperatively the filling pressure was raised for the right ventricle and, in many cases, was lowered for the left, compared with normal values. The normal pressure difference between the left and right atrium depends on the difference in resistance between the left and right ventricular circulation, the left ventricle requiring a higher filling pressure than the right ventricle. Also, according to Berglund (1955), at the same filling pressure the stroke volume of the right ventricle exceeds that of the left ventricle. The normal pressure difference between the atria is influenced by the septal defect, and when this defect is sufficiently large, pressure equilibration takes place which is clearly unphysiological in consideration of the normal filling pressure and functional mechanism of both the right and the left ventricle. These pressure relationships form prerequisite conditions for the occurrence of a left-to-right shunt, but they may also mean some reduction of the filling of the left ventricle and the systemic flow.

The postoperative pressure reduction was most pronounced in the right ventricle (***), right atrium (**) and in the pulmonary artery (*), while the mean PCV pressure showed no significant change, and therefore the pressure gradient across the pulmonary capillary bed remained essentially unaltered and independent of the pulmonary blood flow. However, among the older patients with large left-to-right shunts preoperatively, there was a tendency towards higher mean PCV pressures postoperatively. This was probably an expression of increased filling pressure of the left ventricle.

The frequency of pulmonary hypertension reported in ASD sec. varies considerably, due mainly to differences in definition and in the composition of the series of patients described. Besterman (1961) found a frequency of 16 % with systolic PA pressure equal to or higher than 50 mm Hg, among a series of 225 ASD sec. Derra et al. (1965) found from literature reports a frequency varying between 13 and 25 %. Only 3 patients (2.6 %) in the present series had pulmonary hypertension, which thus seems a remarkably low frequency. The frequency of pulmonary hypertension increases with advancing age, and in addition, recurrent upper respiratory infections probably play an important role (Besterman

at the follow up examination, and was significantly higher (***) than preoperatively The preoperative value, which lay at the lower normal limit may thus have been an expression of increased peripheral utilization of the oxygen content of the blood, which may be associated with so called hypokinetic circulation.

Jonsson et al. (1957) in particular have discussed the relationship between the size of the left-to-right shunt and the degree of roentgenological cardiac enlargement as an expression of the adaptation of the right heart to the shunt. Davidsen (1960) and Derra et al. (1965) and also Zaver and Nadas (1965) have reported this relationship Kjellberg et al (1959) Reindell et al. (1962) and Zaver and Nadas (1965) found, however a normal heart volume in 8—12 % of their cases, thus being *somewhat more frequent in children and* young adults. According to Bedford et al. (1957) increasing age is accompanied by a tendency to increasing heart volumes. Davidsen (1960) found that pronounced cardiac enlargement above that which can be explained by the shunt, was prognostically unfavourable, and was usually an expression of myocardial and/or valvular disorders.

A normal heart volume preoperatively need not, however exclude the existence of a relationship between shunt magnitude and heart size. The shunt volume involves the right atrium and ventricle, where a large shunt volume should cause more *pronounced enlargement* than a small volume, under conditions similar in other respects (myocardial function flow resistance) Conceivably therefore, the total relative heart volume could be normal in such cases where the left ventricle, perhaps because of lack of physical training, is relatively smaller than normally (Jonsson 1966) After the operation a volume reduction may then be an expression of flow reduction in the right heart.

At the follow-up examination, however no statistically certain correlation was found, in the present series, between shunt reduction and reduction of the relative heart volume or systolic right ventricular pressure, in the different age groups.

Some overrepresentation of large left-to-right shunts in older patients can be explained by the fact that these patients had had symptoms which led to cardiological investigation.

The postoperative pressure reaction at rest in the pulmonary circulation was in accordance with previous *findings*, and involved a reduction from slightly raised or high normal pressure levels to normal values (Kirklin et al. 1956) This can be considered to agree with the haemodynamic mechanism in patients with uncomplicated secundum defects, and can be explained by the hyperkinetic effect of the left-to-right shunt which results in a pressure increase to high normal values but not usually to values that are pathologically raised

The pressure difference between the atria in uncomplicated atrial septal defect has been described by Kjellberg et al. (1959) among others, and in the present series this was, on the average, 1.5 mm Hg The mean pressure in both the right and the left atrium and also the mean PCV pressure were somewhat

Haemodynamic findings at rest and during exercise in 51 patients at follow up examination

In 51 patients pressure and flow determinations were made both at rest and during exercise on recatheterization.

These patients (5 girls and 6 boys in age group A, 18 women and 5 men in age group B, and 15 women and 2 men in age group C) showed no essential difference clinically or at rest haemodynamically from the other patients of the series either preoperatively or at the follow-up examination about 18 months after the operation. The results for this group have been compared with values for young normal persons given by Holmgren, Jonsson and Sjöstrand (1960) and Bevegård, Holmgren and Jonsson (1960) and for older normal persons by Granath, Jonsson and Strandell (1964) and Malmborg (1964).

Of the remaining 56 patients, of whom 39 were children, exercise tests during recatheterization were either not carried out, for various reasons, or were unsatisfactory.

The results obtained on cardiac catheterization at rest and during exercise are summarized in Tables 14 and 15 and Figs 9—14. In view of the differences in haemodynamic conditions in children, women and men, the results for the different age groups are reported separately.

Circulatory function

Heart rate At rest the heart rate in the children was, on the average, 81 beats per minute, in the women in age groups B and C 72 beats per minute and in the men in age groups B and C 63 beats per minute. One girl in age group A with a heart rate of 48 had an A V block II the block being constantly 2 1 One woman with atrial fibrillation had a relatively regular slow ventricular frequency (73/min) In all other cases there was sinus rhythm with a normal frequency

Oxygen uptake At rest the oxygen uptake in the children, women and men was, on the average, 2.8 % 18.6 % and 12.4 % higher respectively than the basal oxygen uptake In the women and men the basal metabolic rate lay within the normal limits this was not investigated in the children. In no case were any clinical signs of thyroid dysfunction seen.

On cardiac catheterization during exercise the oxygen uptake increased to normal extent with increasing work loads. The mean val for the degree of mechanical efficiency was 20 % in the children and women and 22 % in the men, at a work load which increased the heart rate to an average of 134 beats/min, 134 beats/min and 123 beats/min, respectively in these three groups.

1961) In the present series only 4 patients were over 50 years of age, and there was no tendency to recurrent upper respiratory infections which may explain, at least partly the low incidence of pulmonary hypertension

No correlation was found in the present series between the size of the left-to-right shunt and the pressure gradient between the right ventricle and pulmonary artery This gradient was probably caused by the preoperatively increased flow due to the effect of "pressure loss of velocity" (Jonsson 1957)

Summary

The oxygen saturation and pressure conditions at rest before and on the average, 17 months after surgical repair of ASD sec in 107 patients are reported.

The left-to-right shunt was preoperatively on the average, 61 % of the pulmonary blood flow No significant correlation was found between the size of the left-to-right shunt expressed in % of the pulmonary blood flow and the preoperative roentgenological heart volume expressed in ml/m² body surface area, in any of the age groups. No residual shunts were found on recatheterization. The oxygen saturation in the superior vena cava was normal and significantly higher (***) postoperatively indicating preoperatively increased peripheral utilization of the oxygen content. At the follow up examination no statistically certain correlation was found between shunt reduction and reduction of the relative heart volume.

Preoperatively the pressures in the pulmonary circulation were high but within the normal range only three patients had pulmonary hypertension. On recatheterization the pressures were significantly lower in the right atrium (**) right ventricle (***) and the pulmonary artery (*) which shows that preoperatively the left-to-right shunt gave rise to a pressure increase to high normal but not pathological values. Only in the older adults, was there a significant correlation (*) between shunt size and systolic right ventricular pressure. At the follow up examination no statistically certain correlation was found between shunt reduction and reduction of systolic right ventricular pressure, in the different age groups.

The mean PCV pressure was normal and showed no significant change postoperatively and therefore the pressure gradient across the pulmonary capillary bed was essentially independent of the pulmonary blood flow On comparing the filling pressures of the ventricles pre and postoperatively it was found that before the operation, because of the defect this pressure was increased for the right ventricle and in many cases, was decreased for the left, compared with normal values. The pressure relationships and the functional mechanisms of both the right and the left ventricle were unphysiological and were prerequisite conditions for the occurrence of a left-to-right shunt, and possibly also for reduced systemic flow Postoperatively a normal pressure difference between the atria, and prerequisite conditions for normal filling pressure, were noted.

Pressures, mm Hg										Pulm. vasc. resist. (R_p)	Pulm. vasc. resist. index (R_{pi})	Systemic vasc. resist. (R_s)	Systemic vasc. resist. index (R_{si})
RA	RV		PA			PCV	BA						
M	S	D	S	D	M	M	S	D	M				
2.4	[illegible]	2.6	[illegible]	7	[illegible]	3.2	122	68	93	1.4	2.0	20.2	26.1
3.5	29	4.5	31	9	14	8.6	122	63	87	1.8	1.7	19.2	20.4
3.0	[illegible]	3.6	25	8	13	7.1	122	65	90	1.6	1.8	19.6	23.4
[illegible]	18	1.0	15	5	9	2.0	100	50	70	0.8	0.7	14.5	17.5
6.0	35	[illegible]	30	14	17	13.0	140	80	105	3.0	2.9	24.3	31.8
2.1	6.3	1.9	8.7	3.2	4.9	4.7	11.6	15.1	11.7	0.7	0.5	2.9	4.8
0.7	1.9	0.6	2.6	0.9	1.5	1.5	3.5	3.9	3.5	0.2	0.2	0.9	1.5
1.7	[illegible]	1.8	[illegible]	7	12	6.5	134	73	94	1.0	1.4	13.7	21.7
1.2	20	2.4	17	8	10	5.2	136	70	93	0.8	1.5	16.0	31.7
1.0	25	2.8	23	9	15	6.2	143	73	99	1.6	2.5	20.9	33.0
0.5	20	2.2	23	8	13	3.5	140	85	105	1.4	1.6	17.5	23.8
1.4	25	2.3	[illegible]	8	13	6.3	138	73	98	1.3	1.9	18.1	26.8
−2.0	10	−4.0	10	2	7	[illegible]	120	60	70	0.2	0.3	12.6	23.1
6.0	30	8.0	40	11	20	13.0	200	100	140	3.4	5.1	33.4	52.3
2.0	8.2	2.3	6.5	3.4	10.8	2.9	15.3	10.8	14.0	0.9	1.2	4.9	8.3
0.4	1.4	0.4	1.1	0.6	1.8	0.5	2.7	1.8	2.4	0.1	0.2	0.8	1.4
1.0	20	2.3	19	7	11	4.9	137	74	96	1.0	1.5	16.9	29.2
−1.0	15	−1.0	12	2	[illegible]	3.0	120	60	80	0.4	0.5	12.7	22.2
4.0	22	4.0	[illegible]	10	15	7.0	160	80	115	1.9	4.1	22.7	49.0
2.4	4.7	1.3	5.9	2.7	3.0	3.0	12.5	9.3	5.0	0.6	1.1	2.4	10.0
0.9	1.8	0.4	2.2	1.0	1.1	1.1	4.7	3.6	1.5	0.2	0.4	0.9	3.8

Age group A Children up to 15 years
B Women and men 15—29 years
C Women and men 30 years or more

$$R_p = \frac{\bar{P}_{PA} - \bar{P}_{PCV}}{Q} \qquad R_s = \frac{\bar{P}_{BA} - \bar{P}_{RA}}{Q}$$

$$R_{pi} = \frac{\bar{P} \quad - \bar{P}_{PCV}}{Q} \text{ BSA} \qquad R_{si} = \frac{\bar{P}_{BA} - \bar{P}_{RA}}{Q} \text{ BSA}$$

In most cases during exercise the saturation decreased to a normal extent with increasing work load and heart rate but to values which lay at the lower normal limit. Three patients in age group B showed a rather high oxygen saturation at rest, but this decreased to a normal extent during exercise. A girl in age group A with an A-V block II (2 1) showed a normal reduction of the

Table 14 Observations during heart catheterization *at rest* in 51 pat. at the follow-up examination

Age groups and sex	Characteristic	No.	Heart rate, beats/min	Oxygen saturation per cent BA	Oxygen saturation per cent PA	AVD ml/l	Oxygen uptake ml/min STPD	Cardiac output l/min	Cardiac index l/min per m BSA	Stroke volume ml	Stroke volume index ml/m BSA
A Girls	mean	5	6	97 9	72.6	41.5	183	4 4	3 6	61	47
Boys	»	6	[illegible]	96 6	75 1	37.2	167	4.5	4 1	[illegible]	51
Total	»	11	81	97.3	74 0	39.2	174	4.3	3.8	57	49
	min		46	94 0	69 1	30 0	149	3.8	2.8	42	37
	max.		107	99.2	77 0	44 0	203	5.5	5.7	98	[illegible]
	SD		14 8	1 8	3 6	4 4	12.3	0.7	0.9	16.4	9.3
	SE		4 4	0.5	1 7	1.3	3.7	0.2	0.3	4.9	2.8
B Women	mean	18	70	98 4	72.2	39 4	221	5 7	3.5	84	51
Men	»	3	63	99 4	74 0	47.3	275	3.9	3 1	91	47
C Women		15	76	98.6	68.1	45.3	218	4.9	3 0	66	41
Men	»		62	97.9	70.5	44.5	206	6.0	3 0	96	48
B+C Women	mean	33	72	98.5	69 1	41.2	219	5.5	3.3	76	45
	min		48	96.7	58.2	30.5	158	3.5	2.3	48	35
	max.		102	100.0	81 7	55.8	281	8.3	4 7	129	62
	SD		12.3	1.3	4 0	6.7	27.2	1.2	0.8	19.2	4 4
	SE		2 1	0.2	0.7	1 1	4 7	0.2	0 1	3.3	0.8
B+C Men	mean	7	63	98.9	73.0	46.5	273	5.9	3 1	92	48
	min.		52	95.8	70 4	36 1	253	5 1	2.7	74	37
	max.		73	100 0	81 9	53.9	295	7 0	4 1	96	60
	SD		8.5	1 7	4.2	5.2	14.3	0 6	0 6	14 1	9.5
	SE		3.2	0 6	1.6	1.9	5 4	0.2	0.2	5.3	3.6

RA = right atrium
RV = right ventricl
PA = pulmonary artery
BA = brachial artery
PCV = pulmonary capillary venous pressure
S = systolic pressure
D = diastolic pressure
M = mean pressure
AVD = arteriovenous oxygen difference

Arterial oxygen saturation The arterial oxygen saturation lay within the normal limits both at rest and during exercise. At rest the mean value was, on the average, 98.1 and during exercise somewhat lower 97 3

Oxygen saturation of mixed venous blood (Fig 9) At *rest* the mean oxygen saturation of mixed venous blood drawn from the pulmonary artery was, on the average 71 7

Pressure, mm Hg										Pulm vasc. resist. (R_P)	Pulm vasc. resist. index (R_{AP})	Systemic vasc. resist. index (R_S)	Systemic vasc. resist. index (R_{AS})
RA	RV		PA			PCV	BA						
M	S	D	S	D	M	M	S	D	M				
2 7	36	2.6	34	13	22	[illegible]	160	81	108	1 7	2.3	13.8	17.2
2 9	36	4.5	33	16	21	10.3	148	82	102	1.5	1 6	13.5	14.3
2.4	36	3.7	34	15	[illegible]	9.6	152	81	104	1.6	1.8	13.6	15.7
1	30	1	23	3	17	9	130	60	90	0.1	0.2	11.3	10 7
11	47	7	47	20	30	17	175	90	120	3.5	4.3	15 1	20.0
1 4	3.1	1.3	7 1	6 6	5 3	3.1	19.5	10.5	11 8	0.9	1 1	1.9	3.2
0.4	1.5	0.5	2 1	2.0	1.6	0.9	5.9	3.2	3.6	0 3	0.3	0.6	1.0
1.6	49	4.2	39	18	23	10.3	174	86	117	1 1	1 7	9.9	16.6
−1.8	[illegible]	1.8	31	10	16	7.6	176	84	110	0.6	1.3	7.9	16.7
0 8	45	3.5	43	18	26	10.2	172	99	131	1.8	3.0	14.6	23.7
2 0	56	2 0	47	23	25	11.5	202	97	127	1 1	2.3	10 7	22.2
1.2	47	[illegible]	40	17	24	10.5	182	91	122	1 4	2.2	11 7	19.6
−4	[illegible]	−6	27	7	14	1	110	55	75	0.2	0.4	6.2	9.2
10	95	15	60	[illegible]	43	18	240	140	180	4.2	6.7	27.6	42.0
2 6	12 0	1.9	9 8	5.9	[illegible]	5 4	29.4	5.1	21 7	0 8	1.3	3.5	3.1
0 4	2.1	0 3	1 7	1.0	1.5	0.9	5.1	0.9	3.8	0.1	0.2	0.6	0.5
−0.7	40	1.9	33	14	19	8.7	182	88	115	0.9	1 4	8.7	18.3
−4	30	−3	23	5	15	6	140	70	85	0.3	0.5	4.2	7.9
[illegible]	[illegible]	4	33	32	25	12	240	105	150	1 3	2.7	12.4	26.3
4.2	4.8	3.2	3.3	4 1	3.4	2.3	10.0	18.2	23.2	0.3	0.5	2.4	5.5
1 6	1.8	1 1	1.2	1.3	1.3	0.9	3 6	6.9	8.7	0.1	0.2	0.9	2.1

both at rest and during exercise. In relation to the oxygen uptake most patients showed, during exercise a somewhat high arteriovenous difference which was not quite parallel with the normal curvilinear regression line In relation to the heart rate most patients showed a normal increase of the arteriovenous oxygen difference during exercise

Cardiac output (Fig 12 A—C) At rest the mean cardiac output in age group A was 4 5 l min, with no difference between boys and girls. In the women of age group B this value was 5 7 l/min, and in those of age group C, 4.9 l/min. The corresponding values for cardiac index were 3.8, 3.5 and 3 0 l/min per m² body surface area, respectively In the men in age group B the mean cardiac output was 5.9 l/min, and in those of age group C 6.0 l/min, with corresponding cardiac index values of 3.1 and 3.0 l min per m² body surface area, respectively The cardiac index

Table 15 Observations on heart catheterization during work in 51 pat. at the follow-up examination.
Abbreviations as in Table 14

Age groups and sex	Characteristic	No.	Work load kpm/min	Heart rate, beats/min	Oxygen saturation per cent BA	Oxygen saturation per cent PA	AVD ml/l	Oxygen uptake ml/min STPD	Cardiac output l/min	Cardiac index l/min per m BSA	Stroke volume ml	Stroke volume index ml/m BSA
A Girls	mean	5	250	132	96.8	41.9	92.0	784	8.4	6.6	74	[illegible]
Boys	»	6	250	135	96.5	42.5	90.0	691	7.7	7.0	57	53
Total	»	11	250	134	96.7	43.7	91.0	734	8.0	6.8	65	[illegible]
	min.			66	95.6	28.6	71.8	560	6.7	5.1	41	38
	max			164	99.3	53.9	117.3	1 045	10.6	8.3	62	93
	SD			28.9	1.3	7.4	13.0	175.7	1.4	1.3	32.3	1.8
	SE			8.5	0.4	2.2	3.9	52.9	0.4	0.4	9.7	0.5
B Women	mean	18	400	142	97.5	44.6	94.6	1 163	12.2	7.3	87	53
Men	»	5	600	123	98.0	48.2	108.9	1 519	13.9	7.2	112	55
C Women	mean	15	300	127	97.7	43.5	96.7	914	9.4	5.7	76	46
Men	»	2	500	122	96.2	43.6	112.2	1 370	12.0	5.2	98	48
B+C Women	mean	33	350	134	97.6	44.1	95.5	1 080	10.9	6.7	82	50
	min.			76	94.3	29.3	78.4	437	5.1	4.3	42	27
	max.			171	100.0	66.4	120.1	1 782	17.0	9.8	133	85
	SD			25.3	4.9	5.9	14.6	282.1	2.3	1.7	19.6	3.8
	SE			4.4	0.8	1.0	2.5	49.0	0.4	0.3	3.4	0.7
B+C Men	mean	7	550	123	97.5	46.9	109.7	1 476	13.3	6.9	108	53
	min.			100	95.2	41.2	93.7	996	10.1	4.7	84	40
	max.			150	100.0	55.6	123.0	2 211	20.3	10.7	135	70
	SD			18.7	3.7	2.2	7.9	412.6	3.0	1.8	16.0	8.3
	SE			7.1	1.4	0.8	3.0	155.7	1.1	0.7	6.0	3.1

oxygen saturation on increase of the heart rate from 48 beats/min at rest to 66 during exercise. One woman in age group C with normal resting values showed a negligible saturation reduction in relation to the heart rate. The lowest value was noted in a boy in age group A (28.6 %). During exercise no difference in the oxygen saturation in mixed venous blood was found between the different age groups.

Arteriovenous oxygen difference (Figs. 10 and 11). At *rest* the mean arteriovenous oxygen difference (AVD ml/l) was, on the average 39.2 ml/l in children, 41.2 ml/l in women and 46.5 ml/l in men. 15 patients showed values higher than 45 ml/l.

During *exercise* the values increased with increasing work loads, and varied between 71.8 and 123.0 ml/l. The arteriovenous oxygen difference values have been plotted against oxygen uptake in Fig. 10 and against heart rate in Fig. 11.

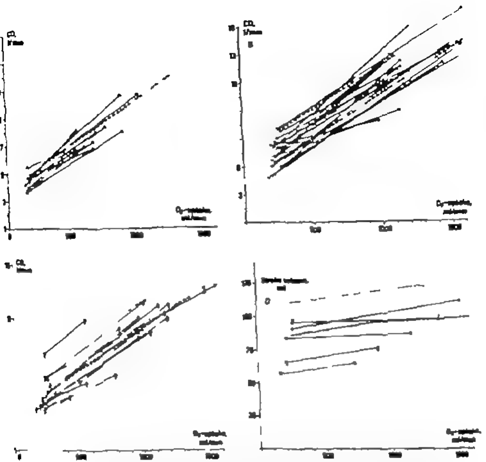

Fig. 12. Oxygen uptake (ml/min) in relation to cardiac output (l/min) at rest and during exercise. Regression lines for cardiac output on oxygen uptake in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964). Symbols as in Fig. 9.

Fig. 12 A shows the conditions for 11 children in age group A,

Fig. 12 B for 18 females and 3 males in age group B, and

Fig. 12 C for 15 females and 2 males in age group C.

In Fig. 12 B and C (see arrows) there was no room for three symbols, representing cardiac output values of 14.8, 15.5 and 14.0 l/min, and oxygen uptake values of 1790, 2140 and 1720 ml/min.

Fig. 12 D. Mean stroke volume (ml) in relation to oxygen uptake (ml/min) at rest and during exercise. Mean stroke volumes in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964). Squares represent children. Other symbols as in Fig. 9.

mm Hg in the women and 1.0 mm Hg in the men.

During exercise this value decreased to 4 mm Hg and –0.7 mm Hg, respectively.

These values, both at rest and during exercise, lay within the normal limits of variation.

Right ventricle. At rest the systolic pressure in the right ventricle was, on the

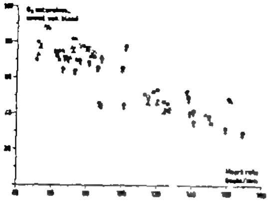

Fig 9 Oxygen saturation of mixed venous blood (in pulmonary artery) in per cent, in relation to heart rate (beats/min) at rest and during exercise. Circles represent women, triangles men open symbols = children, filled symbols = patients in age group B. Circles with crosses, and triangles with arrows represent patients in age group C.

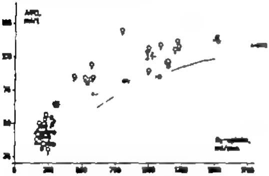

Fig 10. Arteriovenous oxygen difference (AVD) ml/l in relation to oxygen uptake, ml/min, at rest and during exercise. *Central line indicates* regression between these parameters, interrupted lines ± tandard error of estimate for normal persons according to Holmgren et al. and Bevegård et al. in Irnell (1964) Symbols as in Fig 9

values at rest lay within the normal limits (See Cullhed 1964 for further references)

During *exercise* the cardiac output in age group A increased to an average of 8 0 l/min. In the women of age groups B and C the values increased to 12.2 and

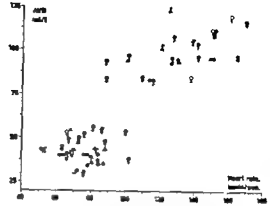

Fig 11 Arteriovenous oxygen difference (AVD) ml/l, in relation to heart rate (beats/min) at rest and during exercise. Symbols as in Fig 9

9 4 l/min and in the men 13.9 and 12.0 l/min respectively

Stroke volume (Fig 12 D) At *rest* the mean stroke volume in age group A was 57 ml with no difference between boys and girls. In the women of age groups B and C the stroke volumes were 84 and 66 ml, and in the men 91 and 96 ml, respectively The stroke volumes in the patients of age groups B and C were somewhat lower than the values which have been given for normal persons.

During *exercise* the stroke volume in age group A increased by an average of 8 ml. In age groups B and C the increases for the women were 3 ml and 10 ml, and for the men 21 ml and 2 ml, respectively

Intracardiac and intravascular pressures

The results obtained on pressure measurement at rest and during exercise are summarized in Fig 13

Right atrium At *rest* the mean pressure in the right atrium was, on the average, 3 0 mm Hg in the children, 1 4

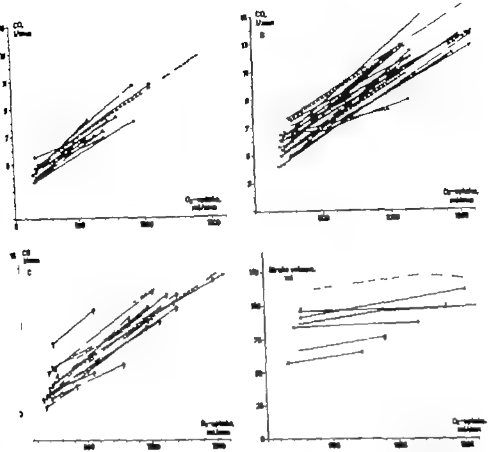

Fig. 12. Oxygen uptake (ml/min) in relation to cardiac output (l/min) at rest and during exercise. Regression lines for cardiac output on oxygen uptake in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964). Symbols as in Fig. 9.

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In Fig. 12 B and C (see arrows) there was no room for three symbols, representing cardiac output values of 14.8, 15.5 and 14.0 l/min, and oxygen uptake values of 1790, 2140 and 1720 ml/min.

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mm Hg in the women and 1.0 mm Hg in the men.

During *exercise* this value decreased to 2.4 mm Hg and –0.7 mm Hg, respectively.

These values, both at rest and during exercise, lay within the normal limits of variation.

Right ventricle. At *rest* the systolic pressure in the right ventricle was, on the

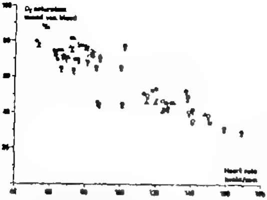
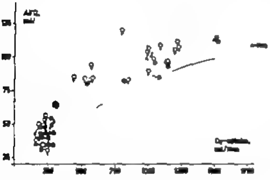


Fig 9 Oxygen saturation of mixed venous blood (in pulmonary artery) in per cent, in relation to heart rate (beats/min) at rest and during exercise. Circles represent women, triangles men open symbols = children, filled symbols = patients in age group B. Circles with crosses, and triangles with arrows represent patients in age group C.



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During *exercise* the cardiac output in age group A increased to an average of 8 0 l/min. In the women of age groups B and C the values increased to 12.2 and

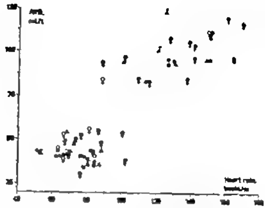

Fig 11 Arteriovenous oxygen difference (AVD) ml/l, in relation to heart rate (beats/mm) at rest and during exercise. Symbols as in Fig 9.

9 4 l/min, and in the men 13.9 and 17 0 l/min, respectively

Stroke volume (Fig 12 D) At *rest* the mean stroke volume in age group A was 57 ml, with no difference between boys and girls. In the women of age groups B and C the stroke volumes were 84 and 66 ml, and in the men 91 and 96 ml, respectively The stroke volumes in the patients of age groups B and C were somewhat lower than the values which have been given for normal persons.

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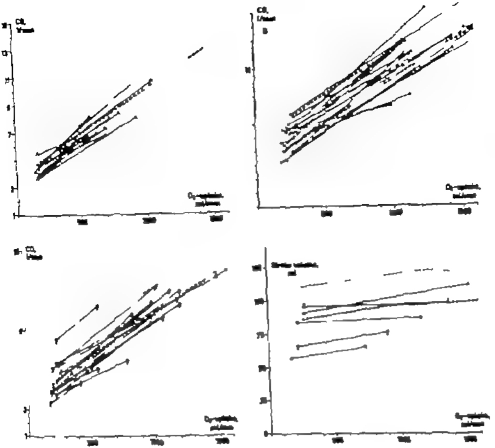


Fig. 12. Oxygen uptake (ml/min) in relation to cardiac output (l/min) at rest and during exercise. Regression lines for cardiac output on oxygen uptake in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964). Symbols as in Fig. 9.

Fig. 12 A shows the conditions for 11 children in age group A,

Fig. 12 B for 18 females and 5 males in age group B, and

Fig. [illegible] C for 15 females and 2 males in age group C.

In Fig. 12 B and C (see arrows) there was no room for three symbols, representing cardiac output values of 14.8, 15.5 and 14.0 l/min, and oxygen uptake values of 1790 2140 and 1720 ml/min.

Fig. 12 [illegible] Mean stroke volume (ml) in relation to oxygen uptake (ml/min) at rest and during exercise. Mean stroke volumes in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964). Squares represent children. Other symbols as in Fig [illegible]

mm Hg in the women and 1.0 mm Hg in the men.

During *exercise* this value decreased to 2.4 mm Hg and −0.7 mm Hg, respectively.

These values, both at rest and during exercise, lay within the normal limits of variation.

Right ventricle. At *rest* the systolic pressure in the right ventricle was, on the

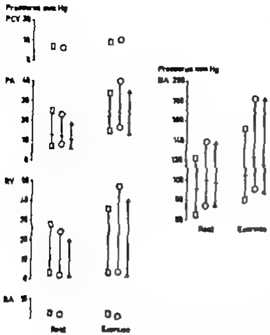


Fig 13. Mean values for pressures, in mm Hg, at rest and during exercise in 11 children (squares) 33 females (circles) and 7 males (triangles) Notation as in Table 14

average, 28 mm Hg in the children, 24 mm Hg in the women and 20 mm Hg in the men. The corresponding figures for end-diastolic pressure were 3 6, 2.3 and 2.3 mm Hg, respectively

During *exercise* these values increased with increasing work loads, to average values of 36 mm Hg in the children, 47 mm Hg in the women and 40 mm Hg in the men. The end-diastolic pressure during exercise was 3 7 mm Hg 3 8 mm Hg and 1.9 mm Hg in the three respective groups.

Pulmonary artery At *rest* the systolic pressure in the pulmonary artery was 25 mm Hg in the children 23 mm Hg in the women and 19 mm Hg in the men. At rest the systolic pressure gradient between the right ventricle and pulmonary artery was 3 mm Hg in the children and 1 mm Hg in the women and men.

During *exercise* the systolic pressure in the pulmonary artery increased in the same way as the systolic pressure in the right ventricle, and in the children this value was now 34 mm Hg in the women 40 mm Hg and in the men 35 mm Hg During exercise, the systolic pressure gradient in the children was 2 mm Hg, in the women 7 mm Hg and in the men 4 mm Hg

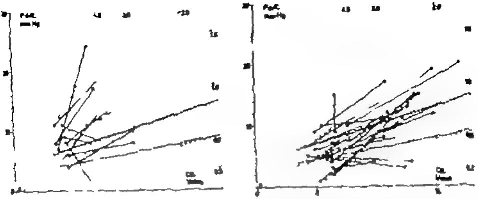
The mean pressure in the pulmonary artery at rest was 13 mm Hg in the children 13 mm Hg in the women and 11 mm Hg in the men. During exercise these values increased to 22, 24 and 19 mm Hg respectively

Pulmonary capillary venous pressure At *rest* the mean PCV pressure was 7 1 mm Hg in the children, 6.3 mm Hg in the women and 4.9 mm Hg in the men. The highest mean PCV pressure was 13 mm Hg

During *exercise* these values increased to 9 6, 10.3 and 8.7 mm Hg respectively The highest value during exercise was 18 mm Hg

Brachial artery At *rest* the systolic pressure was, on the average, 122 mm Hg in the children, 138 mm Hg in the women and 137 mm Hg in the men. The corresponding mean pressure values were 90 98 and 96 mm Hg Two women in age group C had moderate arterial hypertension with systolic pressures of 185—200 and diastolic pressures of 100 mm Hg

During *exercise* the systolic pressure increased to 152 mm Hg in the children and 182 mm Hg in the women and men. The mean pressure values for these three groups were 104 1.2 and 115 mm Hg, respectively The highest values for systol



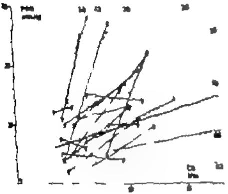


Fig. 14. Relationship between pressure gradient (Pdiff) across the pulmonary vascular bed, in mm Hg, and cardiac output (CO) l/min, at rest and during exercise. Pdiff expressed as the difference in mean pressure between PA and PCV in mm Hg. Very thin broken lines represent different isoresistance lines (R). The other broken lines are regression lines for these parameters for old (heavy lines) and young (thin lines) normal persons according to Granath et al. (1964). Symbols as in Fig. 9. Fig. 14 A shows the conditions in age group A, Fig. 14 B in age group B and Fig. 14 C in age group C.

le pressure during exercise, i.e. 240 and 270 mm Hg, were recorded in the two women who had shown raised pressure at rest.

Pulmonary vascular resistance (R_p, Fig. 14). At rest the pulmonary vascular resistance, expressed as mm Hg per l/min, was on the average, 1.6 in the children, 1.3 in the women and 1.0 in the men. The corresponding values for pulmonary vascular resistance index (R_{I_p}) expressed as mm Hg per l/min × m² body surface area were 1.8, 1.9 and 1.5 respectively. These mean values were within the normal limits, but in the older women, in particular, a tendency to an increased pulmonary vascular resistance was seen.

During *exercise* the pulmonary vascular resistance decreased in approximately one half of the patients, but large individual variations were noted in the different age groups. Compared with the resistance at rest, no statistically significant change was noted during exercise.

Systemic vascular resistance (R_s). At rest, the systemic vascular resistance, expressed as mm Hg per l/min, was, on the average, 19.6 in children, 18.1 in women and 16.9 in men. The corresponding values for systemic vascular resistance index (R_{I_s}) expressed as mm

Hg per l/min × m^2 body surface area were 23.4 26.8 and 29.2 respectively These values lay within the normal limits except in the two patients with arterial hypertension.

During *exercise* the systemic vascular resistance decreased to an essentially normal extent.

Discussion

Up to the present time no reports appear to have been made which have illustrated the haemodynamic conditions both at rest and during work in patients with surgically repaired secundum defects. It seemed of interest therefore, to study these conditions in a series of patients 18 months, on the average, after open repair of a haemodynamically uncomplicated secundum defect, where both the operation and the postoperative course were free of complications.

From a clinical aspect it is important to know not only that the defect is closed but, above all, the general cardiac condition of the patient after the operation. It was therefore of especial interest to determine whether and if so in what way this series of patients with surgically repaired secundum defects differed haemodynamically from normal subjects.

Circulatory efficiency i.e cardiac output in relation to oxygen uptake and heart rate During exercise, the majority of patients showed a somewhat higher arteriovenous oxygen difference than the normal in relation to the oxygen uptake, while, on the other hand the arteriovenous oxygen difference in relation to the heart rate was essentially normal. Since the oxygen uptake and mechanical efficiency were normal, these patients showed on the average, a lower cardiac output during exercise, but this increased, however in a normal way with increasing work loads.

The cardiac output values at rest in the different age groups lay at the lower normal limit, while the cardiac index values were within the normal range of variations. The stroke volume was, on the average, lower than the values reported for young healthy persons, and was in closer agreement with the conditions seen in older healthy men. During exercise, however the stroke volume increased to a normal extent, following in the main the values given for normal persons.

Patients with a low cardiac output in relation to the oxygen uptake, and a high arteriovenous oxygen difference in relation to the heart rate are designated as having a hypokinetic circulation, in contrast to those with a hyperkinetic circulation as pointed out e.g by Holmgren et al. (1957) A tendency to hypokinetic circulation has been demonstrated in elderly normal men, by Strandell (1964) and in asthmatic patients by Irnell (1964) In both of these series an increase in the arteriovenous oxygen *difference in relation to the oxygen uptake*, and also a reduction of the maximal heart rate, were observed with advancing age, and this resulted in a tendency to an increase in the arteriovenous difference in relation to the heart rate.

The results of the haemodynamic studies in patients with surgically repaired secundum defects were *in* close agree-

ment with the conditions in hypokinetic circulation. On the other hand, in most cases the arteriovenous difference was normal in relation to the heart rate, and therefore from this point of view these patients could be said to have a normokinetic circulation.

On making comparisons with the normal values given, consideration should be taken, not only of age, but also of the fact that these normal values are based on investigations in men, while the present series is comprised predominantly of women, in whom the circulatory efficiency may be different.

The pressures at rest in the pulmonary circulation and PCV were normal, and on the average somewhat higher in the children than in the women and men. The pressure in the brachial artery was normal in the children and adults.

During exercise the pressures increased to an essentially normal extent. The pressure increases were somewhat more pronounced in the older patients compared with the children the pressure difference between the young and older patients during exercise was in agreement with the findings of Granath et al. (1964) and may be explained by age-dependent structural changes with increasing vascular rigidity. In these patients, who before the operation, because of the left-to-right shunt, showed greatly augmented pulmonary blood flow the elasticity function in the main branch of the pulmonary artery may have been reduced. Such vascular changes are probably more pronounced in older than in young patients, and may then produce a tendency to reduced pressure tolerance, especially during exercise. The mean PCV pressure increased to a normal extent during work, this increase being somewhat higher in older than in young patients. This was in accordance with previous findings, and was probably due to the fact that the filling pressure in the left ventricle increases to some extent during exercise with advancing age (Granath et al. 1964).

The mean values for pulmonary vascular resistance were within the normal limits both at rest and during exercise, but there was a tendency to high normal or raised values among the older patients. This is explained by the fact that in these patients the pressure gradient across the pulmonary vascular bed was high, while, on the other hand, the pulmonary blood flow was low.

With a few isolated exceptions, the pressures in the brachial artery were normal both at rest and during exercise. The systemic vascular resistance was also normal both at rest and during exercise.

Summary

The haemodynamic findings at rest and during exercise are reported for 51 patients catheterized approximately 18 months after surgical repair of haemodynamically uncomplicated ASD sec. The pre- and postoperative values at rest in these patients showed no deviation from the results discussed previously for the entire series.

It was of especial interest to study the circulatory efficiency i.e. the cardiac output in relation to the oxygen uptake and heart rate. The results appeared to agree with the conditions in hypokinetic

Hg per l/min × m² body surface area, were 23.4, 26.8 and 29.2 respectively. These values lay within the normal limits except in the two patients with arterial hypertension.

During exercise the systemic vascular resistance decreased to an essentially normal extent.

Discussion

Up to the present time no reports appear to have been made which have illustrated the haemodynamic conditions both at rest and during work in patients with surgically repaired secundum defects. It seemed of interest, therefore, to study these conditions in a series of patients 18 months, on the average, after open repair of a haemodynamically uncomplicated secundum defect, where both the operation and the postoperative course were free of complications.

From a clinical aspect it is important to know not only that the defect is closed but above all the general cardiac condition of the patient after the operation. It was therefore of especial interest to determine whether and if so in what way this series of patients with surgically repaired secundum defects differed haemodynamically from normal subjects.

Circulatory efficiency, i.e. cardiac output in relation to oxygen uptake and heart rate. During exercise, the majority of patients showed a somewhat higher arteriovenous oxygen difference than the normal in relation to the oxygen uptake, while, on the other hand, the arteriovenous oxygen difference in relation to the heart rate was essentially normal. Since the oxygen uptake and mechanical efficiency were normal, these patients showed, on the average, a lower cardiac output during exercise, but this increased however in a normal way with increasing work loads.

The cardiac output values at rest in the different age groups lay at the lower normal limit, while the cardiac index values were within the normal range of variations. The stroke volume was, on the average, lower than the values reported for young healthy persons, and was in closer agreement with the conditions seen in older healthy men. During exercise, however, the stroke volume increased to a normal extent, following in the main the values given for normal persons.

Patients with a low cardiac output in relation to the oxygen uptake, and a high arteriovenous oxygen difference in relation to the heart rate, are designated as having a hypokinetic circulation, in contrast to those with a hyperkinetic circulation as pointed out e.g. by Holmgren et al. (1957). A tendency to hypokinetic circulation has been demonstrated in elderly normal men, by Strandell (1964), and in asthmatic patients by Irnell (1964). In both of these series an increase in the arteriovenous oxygen difference in relation to the oxygen uptake, and also a reduction of the maximal heart rate, were observed with advancing age, and this resulted in a tendency to an increase in the arteriovenous difference in relation to the heart rate.

The results of the haemodynamic studies in patients with surgically repaired secundum defects were in close agree

CHAPTER IX

Haemodynamic findings at rest and during exercise before and after operation in 18 patients

In 18 patients the pressure and flow determinations during exercise were carried out with the same work load before as after operation, and therefore in this series individual comparisons of certain haemodynamic functions could be made. These results are therefore reported separately.

In this small series no consideration has been taken of the sex differences in the young and older adults. In age group A there were 6 children (3 boys and 3 girls). In age group B, the young adults, there were 5 women and 2 men, and in age group C, the older adults, 4 women and 1 man. These patients were examined 11 months, on the average, after operation. The results from these investigations are summarized in Tables 16 and 17 and Figs. 15—23.

Circulatory function

Heart rate. The heart rate was essentially the same at the follow-up examination as before operation. In the children an average value of 87 beats per minute was noted preoperatively and 84 at the follow-up examination, and in the adults 74 and 67 beats per minute, respectively. In all patients sinus rhythm with a normal frequency was noted.

Oxygen uptake (Fig. 15). The oxygen uptake at rest was the same on recatheterization as preoperatively in all age groups.

During *exercise* this value rose to a normal extent with increasing work loads in the different age groups, the increase being approximately the same preoperatively *as on recatheterization.* The relationship between heart rate and oxygen uptake was also the same on both these occasions. The mean value for the mechanical efficiency was 18 % in the children, 22 % in the young adults and 21 % in the older adults, at a work load which increased the heart rate both pre- and postoperatively to 144 beats/min on the average in the children and 128 beats/min and 111 beats/min in the other two groups, respectively.

Arterial oxygen saturation. The arterial oxygen saturation, at *rest* and during *exercise* lay within the normal limits both preoperatively and on recatheterization. At rest, the mean arterial oxygen saturation in the entire series was 97.9 %, and during exercise 96.5 % with no difference between the age groups.

Oxygen saturation in superior vena cava (Fig. 16 A). At *rest* the mean oxygen saturation of blood drawn from the superior vena cava was, on the average, 71.3 % preoperatively and this remained unchanged (70.1 %) on recatheterization, in the children and young adults. In the older adults of age group C this value *was also* the same

circulation since the majority of patients, especially the children and older adults showed a cardiac output which, at rest, was low though within the normal range, but which increased in a normal way during exercise.

The pressures in the pulmonary circulation were normal at rest, and were, on the average, somewhat higher in children than in adults.

The pressure reaction during exercise was in agreement with previous findings (Granath et al. 1964) this reaction was more pronounced in the older than in the young patients, possibly due to age-dependent structural changes with increasing vascular rigidity and reduced elasticity in the pulmonary artery

The mean PCV pressure was normal both at rest and during exercise the pressure increase during exercise was somewhat more pronounced in the older than in the young patients.

The normal, or somewhat high, pressure gradient across the pulmonary capillary bed with, in many cases, a rather low pulmonary blood flow gave rise to a somewhat high pulmonary vascular resistance both at rest and during exercise, especially in the older patients.

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Heart rate The heart rate was essentially the same at the follow-up examination as before operation. In the children an average value of 87 beats per minute was noted preoperatively and 84 at the follow-up examination, and in the adults 74 and 67 beats per minute, respectively In all patients sinus rhythm with a normal frequency was noted.

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TABLE 16. *Observations during heart catheterization at rest and during work before and after operation in 18 cases with ASD sec.*
Abbreviations as in Table 14

Conditions and age groups		Characteristic	Heart rate, beats/min	AVD ml/l	Oxygen uptake ml/min STPD	Cardiac output l/min Pulm. circ.	Cardiac output l/min Systemic circ.	Cardiac index l/min per m BSA Pulm. circ.	Cardiac index l/min per m BSA Systemic circ.	Stroke volume ml RV	Stroke volume ml LV
Rest											
Preop.	A	mean	87	16.5	167	10.2	3.3	8.7	2.9	119	39
	B	»	73	20.8	234	14.0	5.2	8.4	3.0	191	68
	C	»	76	16.1	[illegible]	15.0	4.0	8.7	[illegible]	204	55
		min.	61	10.0	144	7.9	3.0	5.2	1.5	90	30
		max.	105	49.0	294	18.3	7.5	12.7	3.3	300	89
		SD	10.2	4.6	30.9	2.6	1.1	1.8	0.9	36.9	12.3
		SE	2.4	1.1	[illegible]	0.6	0.3	0.4	0.2	8.7	[illegible]
Post p.	A	mean	84	39.5	174		4.5		3.6		55
	B	»	63	40.4	34		5.9		3.6		94
	C	»	71	49.5	220		4.5		2.6		61
		min.	50	31.3	149		3.5		2.3		44
		max.	107	55.8	29		7.7		4.5		110
		SD	9.2	5.7	30.9		0.8		[illegible]		11.4
		SE	2.2	1.3	7.3		0.2		0.1		0.3
Work											
Preop	A	mean	150	46.5	642	13.9		12.2		95	
	B	»	130	31.1	1152	23.4		14.5		181	
	C	»	112	43.0	766	19.9		11.4		177	
		min.	85	32.9	540	10.6		8.9		2 8	
		max.	170	67.3	1644	34.0		21.0		72	
		SD	20.4	10.2	261.3	6.9		2.9		34.1	
		SE	4.9	2.4	61.6	1.6		0.7		8.0	
Postop	A	mean	138	83.5	644		7.7		6.0		56
	B	»	126	92.3	1280		13.4		7.8		105
	C	»	110	93.5	773		8.2		4.5		73
		min.	88	43.0	437		3.1		3.4		43
		max.	170	120.1	1644		17.0		9.8		133
		SD	20.3	17.1	234.1		[illegible]		1.3		[illegible]
		SE	4.8	4.1	55.2		0.5		0.3		3.1

$$W_{I_{RV}} = \frac{C_{I_P}\ 1.005\ (\bar{P}_{PA}-\bar{P}_{PCV})\ 13.6}{1000}\ \text{kpm/min per m BSA}$$

$$W_{I_{LV}} = \frac{C_{I_S}\ 1.005\ (\bar{P}_{BA}-\bar{P}_{LA})\ 13.6}{1000}\ \text{kpm/min per m BSA}$$

Stroke volume index (SVI) ml/m BSA RV	LV	Pulm. vasc. resist. Rp	Pulm. vasc. resist. index Ri	Systemic vasc. resist. Rs	Systemic vasc. resist. index R_{i_s}	Work index (Wi) RV	LV	Distensibility index (Di) RV	LV
104	34	0.8	1.0	26.5	31.5	1 1	3.7	20.8	3 0
114	40	0.5	1.0	19 4	32.8	0.9	3.7	26.5	5.0
122	33	1.2	2.2	22.9	40.7	1.5	3.0	30.5	9.0
63	24	0.3	0.5	10	21	0.3	2.1	14	3
185	58	2.1	2.4	32	54	5.8	7.5	103	10
28.7	7.9	[illegible]	0.5	7 7	8 8	1 1	5.1	28.7	2.5
[illegible]	1.8	0.1	0.1	[illegible]	2.1	0.3	1.2	8.8	0.6
	45	1.6	1.9	18.5	23.3	0.4	4.2	14.0	3.5
	54	0.9	1.5	15.4	27.8	0.3	4.6	18.0	6.0
	37	1.8	2.2	19.5	33.0	0.2	3.7	18.5	9.0
	29	0.5	0.7	13	22	0.1	2.8	8	4
	63	3.0	4.8	24	43	0.7	6.0	51	25
	4.5	0.5	0 8	2.5	5.2	0.7	4 4	13.6	8.7
	1 1	0.1	0 2	0.6	1.2	0.2	1 1	3.2	2.1
85		0.8	1 0			2.4		28.3	
103		0.6	1.0			3.0		29 1	
102		1 4	2.3			3.3		20.4	
74		0.4	0 6			0.1		[illegible]	
143		3.1	5.1			4.5		54	
19 4		0 7	0.8			4.7		15.1	
4.6		0.2	0.2			1 1		6.2	
	46	1.6	2.2	13.3	16.9	1.0	8.5	12.8	6.0
	61	0.8	1 4	8.7	15.1	1.3	12.3	17 4	6.5
	42	1.9	3.2	15 0	23.4	0.8	7.3	13.6	4.9
	28	0.1	0.2	7	11	0.3	4.6	4	3
	85	4 1	6.7	17	32	2.7	16.3	43	10
	6.8	0.9	1 4	2.3	3.3	2.8	13.0	12.9	2.8
	2.1	0.2	0.3	0 6	0 6	0.7	3.1	3.5	0.6

$$D_{I_{RV}} = \frac{RV_{SV}}{RV_D}$$

$$D_{I_{LV}} = \frac{LV_{SV}}{LV_D}$$

on both occasions, but somewhat lower viz. 65 4 %

During *exercise* the values decreased in the children and young adults to averages of 63 0 % preoperatively and 55.5 % on recatheterization. In the older adults the corresponding values were 63 1 % and 64.9 % respectively

Oxygen saturation in pulmonary artery (Fig 16 B) At *rest* the mean oxygen saturation in blood drawn from the pulmonary artery was, in the whole series, 88 8 % preoperatively and 72.0 % on recatheterization, with no difference between the age groups.

During *exercise* this value decreased in the whole series to 73 3 % on the average, preoperatively and 47 7 % on recatheterization.

Arteriovenous oxygen difference At *rest* the mean arteriovenous oxygen difference in the whole series was 17 8 ml/l preoperatively with no difference between the age groups. On recatheterization this value was somewhat greater in the older adults (49.5 ml/l) than in the children and young adults (39 9 ml/l)

During *exercise* the arteriovenous oxygen difference increased preoperatively in the whole series to an average of 46 6 ml/l. On recatheterization the value was found to have increased to 83.5 ml/l in the children and to 93 0 ml/l in the adults. In relation to the oxygen uptake most of the older patients showed on recatheterization, during exercise, a rather high arteriovenous oxygen difference, but in relation to the heart rate this increase was essentially normal.

Cardiac output (Fig 17) At *rest* the mean cardiac output in the pulmonary

TABLE 17 Observations during heart catheterization. Abbreviations as in Table 14.

Conditions and age groups		Characteristic	Oxygen saturation per cent BA	PA	SVC
Rest					
Preop.	A	mean	97.9	89 0	71.2
	B	»	99.3	89 6	71 4
	C	»	96.5	87.5	63.3
		min.	90.2	85.6	59.4
		max.	100 0	94.8	85.5
		SD	1.9	2.5	5.6
		SE	0 4	0.6	1.3
Postop.	A	mean	96.8	0.8	70.8
	B	»	97 7	74.5	68.9
	C	»	98.3	0.9	65.6
		min.	95.8	69 6	59 1
		max.	99.9	81.9	75.5
		SD	1 7	3.6	[illegible]
		SE	0.4	0.8	0.8
Work					
Preop.	A	mean	97 1	71 7	63.9
	B	»	98.2	70 4	62.2
	C	»	94 4	79.0	63.1
		min.	84.2	60.0	53.8
		max.	100.0	81 6	70.6
		SD	2.9	4.9	2.9
		SE	0.7	1.2	1.2
Postop.	A	mean	96.6	48.9	54.3
	B	»	97.5	48.0	56.8
	C	»	95.1	46.1	64.9
		min.	93.5	33.5	39.2
		max.	100.0	55.5	75 1
		SD	1 3	6.9	7.2
		SE	0.3	1 6	2.9

circulation before the operation was 10.2 l/min in the children, 14 0 l/min in the young adults and 15 0 l/min in the older adults. The corresponding cardiac index

tion at rest and during work before and after operation in 18 cases with ASD sec.

Pressure, mm Hg									
RA	RV		PA			PCV	BA		
M	S	D	S	D	M	M	S	D	M
3.3	30	5.0	23	8	14	5.3	119	72	90
3.6	30	4.5	23	7	14	6.3	130	71	88
2.0	30	4.0	27	9	[illegible]	5.7	131	74	97
0	22	2	16	4	8	2	100	60	70
4	87	7	87	24	43	11	155	90	110
1.7	13.3	1.9	13.8	3.9	6.5	2.1	12.1	11.7	12.1
0.4	3.2	0.4	3.3	0.9	1.5	0.5	2.8	2.8	[illegible]
2.8	25	3.2	23	7	14	6.9	119	61	83
2.2	25	3.0	24	7	14	8.3	129	65	90
—0.4	[illegible]	2.0	19	6	[illegible]	3.8	139	68	101
—1	18	1	17	5	10	0	110	50	70
5	35	3	34	7	15	17	140	80	100
1.8	6.3	2.1	7.4	3.7	3.2	3.9	9.7	7.6	10.3
0.4	1.5	0.5	1.7	0.9	1.2	0.9	2.3	1.8	[illegible]
0.7	46	3.0	38	13	22	7.5	149	87	98
3.0	41	3.6	40	15	25	9.8	171	80	108
2.3	53	3.0	32	20	32	10.8	168	91	119
—1	33	4	28	10	17	4	140	70	90
9	65	6	100	[illegible]	50	15	210	115	150
2.3	5.8	0.7	7.6	4.4	5.9	3.1	18.4	13.6	20.4
0.9	2.4	[illegible]	1.8	1.1	1.4	0.7	4.3	3.2	4.9
1.6	36	3.7	33	15	[illegible]	8.7	145	82	101
1.6	45	3.5	38	15	23	11.4	172	81	116
0.2	47	2.7	40	17	23	9.4	171	84	115
—3	30	—3	20	3	11	2	150	65	90
10	70	15	60	30	40	20	210	100	160
2.9	9.3	4.3	10.5	8.5	8.4	3.9	16.2	11.2	14.8
0.8	2.7	1.1	2.5	1.5	2.0	0.9	3.9	2.6	3.5

values were 8.7, 8.4 and 8.7 l/min per m² body surface area, respectively.

The mean cardiac output in the systemic circulation was 5.5 l/min in the children, 5.2 l/min in the young adults and 4.0 l/min in the older adults, corresponding to cardiac index values of 2.9, 3.0 and 2.2 l/min per m² body sur-

on both occasions, but somewhat lower viz. 65 4 %

During *exercise* the values decreased in the children and young adults to averages of 63 0 % preoperatively and 55.5 % on recatheterization. In the older adults the corresponding values were 63 1 % and 64.9 % respectively

Oxygen saturation in pulmonary artery (Fig 16 B) At *rest* the mean oxygen saturation in blood drawn from the pulmonary artery was, in the whole series, 88 8 % preoperatively and 72.0 % on recatheterization with no difference between the age groups.

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Cardiac output (Fig 17) At *rest* the mean cardiac output in the pulmonary circulation before the operation was 10.2 l/min in the children, 14 0 l/min in the young adults and 15 0 l/min in the older adults. The corresponding cardiac index

TABLE 17 Observations during heart catheterization. Abbreviations as in Table 14

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Rest				
Preop. A	mean	97.9	89.0	71.2
B	»	99.3	89 6	71 4
C	»	96.5	87.5	65.3
	min.	90.2	85 6	59.4
	max.	*100.0*	*94.8*	85.5
	SD	1.9	2.5	5 6
	SE	0.4	0.6	1.3
Postop. A	mean	96.8	70.8	70.8
B	»	97 7	74.5	68.9
C	»	98.3	70.9	65.6
	min.	95 8	69 6	59 1
	max.	99.9	81.9	75.5
	SD	1 7	3.6	3.3
	SE	0.4	0.8	0.8
Work				
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C	»	94 4	79.0	63.1
	min.	84.2	60.0	53.8
	max.	*100 0*	*81.6*	*70.6*
	SD	2.9	4.9	2.9
	SE	0.7	1.2	1.2
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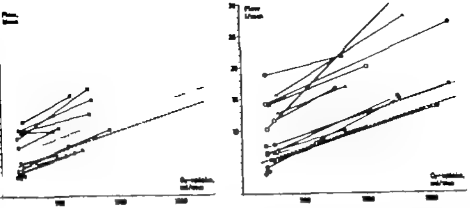
C	»	95 1	46.1	64.9
	min.	93.5	33.5	39.2
	max.	100.0	55.5	75.1
	SD	1.3	6.9	7.2
	SE	0.3	1.6	2.9



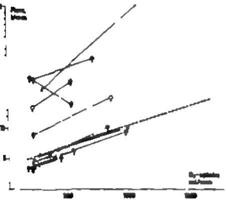


Fig. 17 Oxygen uptake (ml/min) in relation to cardiac output (l/min) in pulmonary and systemic circulation at rest and during exercise before and after operation. Regression lines between these parameters in old (heavy broken line) and young (thin broken line) normal persons according to Granath et al. (1964) Fig. 17 A shows the conditions for 6 children, Fig. 17 B for 5 women and 2 men in age group B, and Fig. 17 C for 4 women and 1 man in age group C. Squares represent children, circles women and triangles men in age group B, and circles with cross women and triangles with an arrow men in age group C. Open symbols = cardiac output in pulmonary circulation; crossed symbols = preoperative and filled symbols postoperative cardiac output in systemic circulation. In Fig. 17 B and 17 C (see arrows in figures) there was no room for two symbols, representing values for cardiac output in pulmonary circulation of 34 and 31.2 l/min and values for oxygen uptake of 1500 and 1120 ml/min, respectively

Shunt group type of defect heart volume and systolic right ventricular pressure 9 patients were in shunt group 2, and 9 in shunt group 3. 16 patients had a large central secundum defect, one child had maximal large, low defect and one patient in age group C had a sinus venosus defect with anomalous right-sided venous return to the superior vena cava. 6 patients had a normal heart volume, 9 patients showed slight cardiac enlargement, and in 3 adults there was moderate or pronounced cardiac enlargement. 11 of the 18 patients showed a systolic right ventricular pressure of 30 mm Hg or more. These haemodynamic and clinical findings were in agreement with those reported for the entire series

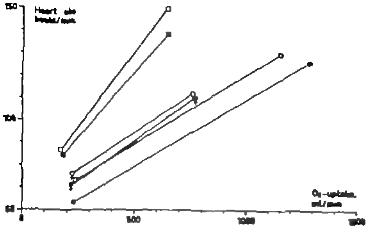


Fig 15 Mean oxygen uptake (ml/min) in relation to mean heart rate (beats/min) at rest and during exercise on catheterization before and after operation. Squares represent children, circles young adults and circles with crosses older adults. Open symbols = preoperative values, filled symbols = post operative values.

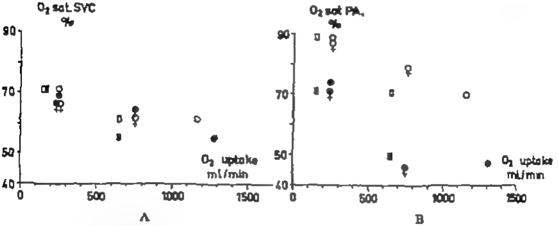


Fig 16. Mean oxygen saturation, in per cent, in relation to mean oxygen uptake, in ml/min, in superior vena cava (SVC, Fig 16 A) and pulmonary artery (PA, Fig 16 B) at rest and during exercise before and after operation. Symbols as in Fig 15

face area, respectively On recatheterization these values were 3 6, 3 6 and 2 6 respectively

During *exercise* the cardiac output in the pulmonary circulation increased by an average of 3 7 l/min in the children, 9 4 l/min in the young adults and 4.9 l/min in the older adults. These increases were normal and were of at least the same order of magnitude as the increases in cardiac output in the systemic circulation noted on recatheterization, except in one patient in age group C who had pulmonary hypertension and showed a reduced cardiac output in the pulmonary circulation preoperatively

The left-to-right shunt at rest was 6.9 l/min in the children, 8.9 l/min in the young adults and 11 0 l/min in the older adults. The corresponding values for shunt index were 5.2, 5 4 and 6.3 l/min per m^2 body surface area, respectively When expressed as per cent of the pulmonary blood flow the shunt was 67 % in the children, 65 % in the young adults and 73 % in the older adults.

In no case was a residual shunt noted on recatheterization.

to 2.0 mm Hg preoperatively and to 1.1 mm Hg on recatheterization.

Right ventricle. At *rest*, the systolic right ventricular pressure in the whole series was 30 mm Hg preoperatively and 24 mm Hg, i.e. significantly lower ( ) on recatheterization. The end-diastolic pressures were 4.4 mm Hg and 2.5 mm Hg, respectively.

During *exercise* the systolic pressure increased both preoperatively and on recatheterization, to averages of 46 mm Hg and 36 mm Hg, respectively in the children, and to 47 mm Hg and 46 mm Hg in the adults. The end-diastolic pressures were 3.7 mm Hg and 3.2 mm Hg, respectively.

Pulmonary artery. At *rest* the systolic pressure in the whole series was, on the average, 24 mm Hg preoperatively and 22 mm Hg on recatheterization. The *diastolic and mean pressures were also* normal, the mean pressures being 15 mm Hg and 13 mm Hg, respectively. The systolic pressure gradient between the right ventricle and pulmonary artery was, at rest 5 mm Hg preoperatively and 2 mm Hg on recatheterization. *One* patient had pulmonary hypertension with a systolic PA pressure of 87 mm Hg.

During *exercise* the systolic pressure in the pulmonary artery increased preoperatively to an a erage of 38 mm Hg in children nd young dults and to 52 mm Hg in older adults. The corresponding mean pressure values were now 23 mm Hg and 32 mm Hg, respectively. On recatheterization the systolic pressures were found to have increased to 37 mm Hg and the mean pressure to 23 mm Hg, in the whole series, with essentially no difference between the age groups.

Pulmonary capillary venous pressure. At *rest* the mean PCV pressure preoperatively was 5.9 mm Hg in the children and young adults and 3.7 mm Hg in the older adults. The corresponding values noted on recatheterization were 7.6 and 3.8 mm Hg, respectively.

During *exercise* the mean PCV pressure increased preoperatively to 7.5 mm Hg in the children and to 10.3 mm Hg in the adults, while the corresponding values obtained on recatheterization were 8.7 and 10.4 mm Hg, respectively.

Brachial artery. At *rest* the systolic pressure in the brachial artery preoperatively was, on the average, 119 mm Hg in the children and 130 mm Hg in the adults, while the mean pressures were 90 mm Hg and 97 mm Hg, respectively. *On recatheterization* no change was noted at rest in these pressures.

During *exercise* the systolic pressures increased to *similar extents* preoperatively and at recatheterization, i.e. to 147 mm Hg in the children and to 170 mm Hg in the adults the corresponding values for the mean pressures being 99 mm Hg and 114 mm Hg, respectively.

Left atrium. The mean pressure in the left atrium was recorded in 14 cases, and was found to be 5.2 mm Hg in the children and young adults, and 2.7 mm Hg in the older adults. The difference in mean pressure between right and left atrium was 1.8 mm Hg in the children and young adults and 0.7 mm Hg in the older adults. The difference between mean PCV pressure and mean pressure in the left atrium was, on the average, 0.8 mm Hg. The preoperative difference

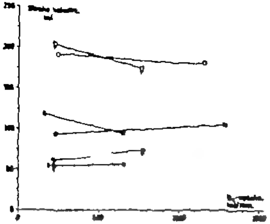


Fig. 18. Mean stroke volume (ml) in relation to mean oxygen uptake (ml/min) at rest and during exercise before and after operation. Crossed symbols = preoperative values for left ventricular stroke volume at rest. Other symbols as in Fig. 15.

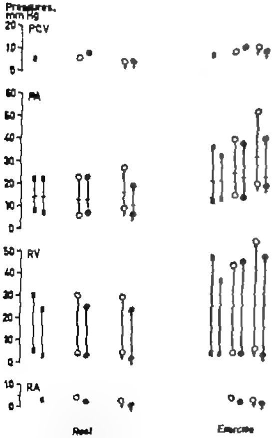


Fig 19 Mean values for pressures at rest and during exercise before and after operation. Notation as in Table 14 and symbols as in Fig 15

of 107 patients. In the small series there was no significant correlation either between the preoperative values of shunt index and heart volume or between their postoperative reductions.

Stroke volume (Fig 18) At *rest* the mean right ventricular stroke volume before operation was 119 ml in the children, 191 in the young adults and 204 ml in the older adults. The corresponding values for the left ventricle were 39, 68 and 55 ml, respectively on recatheterization these values at rest were found to have increased significantly (*) *in the children and young adults (to* 5J ml and 94 ml, respectively) but to have remained essentially unchanged (61 ml) in the older adults.

During *exercise* the right ventricular stroke volume decreased somewhat preoperatively in the children and older adults, but was essentially unchanged in the young adults. On recatheterization no change in the left ventricular stroke volume was observed in the children, compared with the resting value. In the young and older adults increases of 20 % and 10 % respectively of the resting values were noted.

Intracardiac and intravascular pressures

The results of the pressure measurements made preoperatively and at the follow up examination, both at rest and during exercise, are given in Fig 19

Right atrium. At rest preoperatively the mean RA pressure in the whole series was 2.9 mm Hg, and on recatheterization it was significantly (*) lower viz. 1.5 mm Hg

During *exercise* there was a reduction

to 2.0 mm Hg preoperatively and to 1.1 mm Hg on recatheterization.

Right ventricle. At *rest* the systolic right ventricular pressure in the whole series was 30 mm Hg preoperatively and 24 mm Hg, i.e. significantly lower ( ) on recatheterization. The end-diastolic pressures were 4.4 mm Hg and 2.3 mm Hg, respectively.

During *exercise* the systolic pressure increased both preoperatively and on recatheterization, to averages of 46 mm Hg and 36 mm Hg, respectively in the children, and to 47 mm Hg and 46 mm Hg in the adults. The end-diastolic pressures were 3.7 mm Hg and 3.2 mm Hg, respectively.

Pulmonary artery. At *rest* the systolic pressure in the whole series was, on the average, 24 mm Hg preoperatively and [illegible] mm Hg on recatheterization. The diastolic and mean pressures were also normal, the mean pressures being 15 mm Hg and 13 mm Hg, respectively. The systolic pressure gradient between the right ventricle and pulmonary artery was, at rest 5 mm Hg preoperatively and 8 mm Hg on recatheterization. One patient had pulmonary hypertension with a systolic PA pressure of 87 mm Hg.

During *exercise* the systolic pressure in the pulmonary artery increased preoperatively to an average of 38 mm Hg in children and young adults and to 52 mm Hg in older adults. The corresponding mean pressure values were now 23 mm Hg and 32 mm Hg, respectively. On recatheterization the systolic pressures were found to have increased to 37 mm Hg and the mean pressure to 23 mm Hg, in the whole series, with essentially no difference between the age groups.

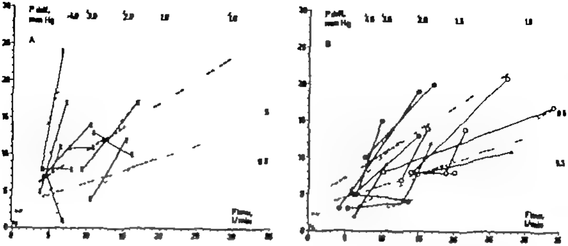
Pulmonary capillary venous pressure. At *rest* the mean PCV pressure preoperatively was 5.9 mm Hg in the children and young adults and 3.7 mm Hg in the older adults. The corresponding values noted on recatheterization were 7.6 and 3.8 mm Hg, respectively.

During *exercise* the mean PCV pressure increased preoperatively to 7.5 mm Hg in the children and to 10.3 mm Hg in the adults, while the corresponding values obtained on recatheterization were 8.7 and 10.4 mm Hg, respectively.

Brachial artery. At *rest* the systolic pressure in the brachial artery preoperatively was, on the average, 119 mm Hg in the children and 130 mm Hg in the adults, while the mean pressures were 90 mm Hg and 92 mm Hg, respectively. On recatheterization no change was noted at rest in these pressures.

During *exercise* the systolic pressures increased to similar extents preoperatively and at recatheterization, i.e. to 147 mm Hg in the children and to 170 mm Hg in the adults, the corresponding values for the mean pressures being 99 mm Hg and 114 mm Hg, respectively.

Left atrium. The mean pressure in the left atrium was recorded in 14 cases, and was found to be 3.2 mm Hg in the children and young adults, and 2.7 mm Hg in the older adults. The difference in mean pressure between right and left atrium was 1.8 mm Hg in the children and young adults and 0.7 mm Hg in the older adults. The difference between mean PCV pressure and mean pressure in the left atrium was, on the average, 0.8 mm Hg. The preoperative difference



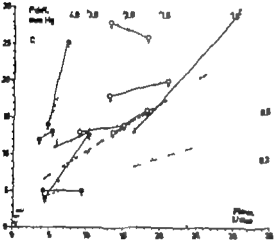


Fig 20 Relationship between pressure gradient (Pdiff) across the pulmonary vascular bed, in mm Hg, and cardiac *output* (CO) *l/min*, at rest and during exercise before and after operation. *Pdiff expressed as the difference in* mean pressure between PA and PCV in mm Hg Very thin broken lines represent different isoresistance lines (R) The other broken lines are regression lines for these parameters for old (heavy lines) and young (thin lines) normal persons according to Granath et al. (1964) Symbols as in Fig 17

Fig 20 A shows the conditions in age group A for 2 children there was no resistance determination during exercise preoperatively Fig. 20 B shows the conditions in age group B, and Fig 20 C in age group C.

in mean pressure between PCV and right atrium was 2.5 mm Hg for the children and young adults and 1 7 *mm Hg for* the older adults. On recatheterization these values were found *to be 5 1* mm Hg and 4.2 mm Hg

Left ventricle The systolic pressure in the left ventricle was 104 mm Hg in the children and young adults and 127 mm Hg in the older adults. The end-diastolic pressures were 7 4 mm Hg and 3 7 mm Hg, *respectively*

Pulmonary vascular resistance (Fig 20) At *rest* the pulmonary vascular resistance was 0 8 in the children, 0 5 in the young adults and 1.2 in the older *adults, preoperatively and 1 6 0.9* and 1 8, respectively on recatheterization. There was thus an average increase in all three groups in the children (**) and young adults (*) this was statistically significant but not in the older adults.

During *exercise* no statistically certain *change* in the pulmonary resistance was noted either preoperatively or at recatheterization, compared with the respective resting values. In one half of the patients a decrease in pulmonary vascular resist

ance was seen, but there were large individual variations.

Systemic vascular resistance. At rest, preoperatively the systemic vascular resistance was 26.5 in the children, 19.4 in the young adults and 22.9 in the older adults, and on recatheterization 18.5, 15.4 and 19.5 respectively. This meant a significantly reduced value in the children (**) but no significant change in the adults.

Ventricular work index (Fig. 21). The ventricular work index (see equation in Table 16) was calculated according to Dexter (1951). For the right ventricular work index a significant (***) reduction was noted on recatheterization, both at rest and during exercise, compared with the preoperative values. The left ventricular work index was significantly ( ) higher postoperatively at rest. Preoperatively the right ventricular work index was somewhat higher in the older than in the young patients, both at rest and during exercise.

Ventricular distensibility index (Fig. 22). The ventricular distensibility index (see equation in Table 16) was calculated according to Rowe et al. (1961) and for the right ventricle this was significantly (**) lower postoperatively than preoperatively both at rest and during exercise.

The distensibility index for the left ventricle was assessed with the reservation that for the postoperative value an approximate value for the left ventricular end-diastolic pressure, calculated from PCV had to be used. The left ventricular distensibility index, at rest, was the same postoperatively as preoperatively and was significantly (***)

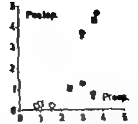


Fig. 21. Ventricular work index at rest and during exercise before and after operation.

Symbols: Squares = children, circles = young adults and circles with cross = older adults. Open symbols = right ventricular work index at rest. Filled symbols = right ventricular work index during exercise. Crossed symbols = left ventricular work index at rest.

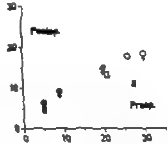


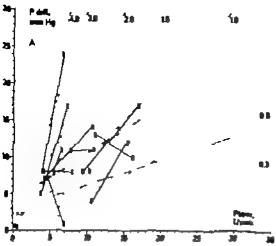
Fig. 22. Ventricular distensibility index at rest and during exercise, before and after operation.

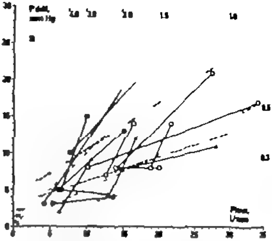
Symbols: Squares = children, circles = young adults and circles with cross = older adults. Open symbols = right ventricular distensibility index at rest. Filled symbols = right ventricular distensibility index during exercise. Crossed symbols = left ventricular distensibility index at rest.

lower than the right ventricular distensibility index.

Discussion

The predominant haemodynamic finding in uncomplicated atrial septal defect of the secundum type is the left-to-right shunt, where a volume corresponding to the size of the shunt is ineffective both





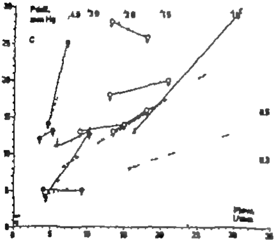


Fig 20 Relationship between pressure gradient (Pdiff) across the pulmonary vascular bed, in mm Hg, and cardiac output (CO) l/min, at rest and during exercise before and after operation. Pdiff expressed as the difference in mean pressure between PA and PCV in mm Hg Very thin broken lines represent different isoresistance lines (R) The other broken lines are regression lines for these parameters for old (heavy lines) and young (thin lines) normal persons according to Granath et al. (1964) Symbols as in Fig 17

Fig 20 A shows the conditions in age group A for 2 children there was no resistance determination during exercise preoperatively Fig. 20 B shows the conditions in age group B, and Fig 20 C in age group C.

in mean pressure between PCV and right atrium was 2.5 mm Hg for the children and young adults and 1 7 mm Hg for the older adults. On recatheterization these values were found to be 5 1 mm Hg and 4 ? mm Hg

Left ventricle The systolic pressure in the left ventricle was 104 mm Hg in the children and young adults and 127 mm Hg in the older adults. The end-diastolic pressures were 7 4 mm Hg and 3 7 mm Hg, respectively

Pulmonary vascular resistance (Fig 20) At *rest* the pulmonary vascular resistance was 0 8 in the children, 0.5 in the young adults and 1.2 in the older adults, preoperatively and 1 6, 0.9 and 1 8, respectively on recatheterization. There was thus an average increase in all three groups in the children (**) and young adults (*) this was statistically significant but not in the older adults.

During *exercise* no statistically certain change in the pulmonary resistance was noted either preoperatively or at recatheterization, compared with the respective resting values. In one half of the patients a decrease in pulmonary vascular resist

at rest was significantly lower preoperatively in the children (**) than at recatheterization, but in the adults it was only slightly lower. Preoperatively, however, in consideration of the cardiac output in the pulmonary circulation the cardiac output in the systemic circulation increased to a probably normal extent during exercise. It may thus be assumed that, in these patients, even before the operation there was a tendency to hypokinetic systemic circulation with a low left ventricular output during exercise.

In order to compare the mechanical efficiency of the ventricles before and after the operation the ventricular work index and distensibility index were calculated. At rest, both these indices showed a significant reduction for the right ventricle on recatheterization. The different haemodynamic parameters which may be related to the left-to-right shunt in atrial septal defect have long been subjected to investigation. Rowe et al. (1961) who studied such parameters at rest, found that the only significant correlation was that between the size of the left-to-right shunt and the difference in distensibility index between the right and left ventricle. In Rowe's study however 4 out of 24 patients had pronounced pulmonary hypertension of the obstructive type, in three cases combined with right-to-left shunt. In the present series there was no correlation between distensibility index and left-to-right shunt.

The shunt volume in atrial septal defect is governed predominantly by the diastolic distensibility of the right ventricle. Dexter (1956) found that the

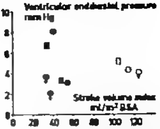


Fig. 23. Ventricular end-diastolic pressure (mm Hg) in relation to ventricular stroke volume index (ml/m body surface area). Squares = children, circles = young adults and circles with cross = older adults. Open symbols = preoperative, and filled symbols = postoperative right ventricular stroke volume index. Crossed symbols = preoperative left ventricular stroke volume index.

capacity of the right ventricle to pump large volumes with a low filling pressure differs somewhat from the conditions in the left ventricle which (according to Starling's law) requires increasing filling pressures for increasing stroke volumes. When, in the present series, the end-diastolic pressure of the right ventricle is plotted against the stroke volume index of the right ventricle, the output of the right ventricle preoperatively is found to be large in relation to the end-diastolic pressure of the right ventricle, which lies at a normal level (Fig. 23). The preoperative end-diastolic pressure in the right ventricle was significantly higher (*) than at the follow-up examination, as also was the mean pressure in the right atrium. These pressures were probably sufficiently high to permit, in view of the distensibility and function curves of the ventricles, a large increase in filling of the right ventricle. The distensibility is determined mainly by the ventricular

as regards oxygen transport and muscular work capacity The left to-right shunt involves, in particular increased work for the right ventricle, while, on the other hand, the work of the left ventricle is unchanged or possibly somewhat reduced with a decrease in the systemic flow

During exercise the size of the left to-right shunt in atrial septal defect cannot be determined with the current methods of blood-gas analysis. An approximate estimate can be made during exercise however At rest the output of the left ventricle is normal or somewhat low while that of the right ventricle is greatly increased. During exercise the output of the right ventricle may increase to a smaller extent than normally and the stroke volume of the right ventricle decreases considerably with the result that the left to-right shunt decreases to the advantage of the left ventricular output which is augmented If the output of the right ventricle increases to a normal extent, it may be expected that the shunt will remain unchanged. If on the other hand the shunt were to increase during exercise this would result in a pronounced increase of the output of the right ventricle. If the left to-right shunt were to decrease greatly or entirely this would result in a reduction of the saturation value in the pulmonary artery to a level which with respect to work, was normal, i.e. 40—50 %

In all but two patients the flow in the pulmonary circulation increased preoperatively during exercise, the exceptions being the patient with pulmonary hypertension and a girl in age group A. Fig 17 shows that in the three age groups this increase was approximately of the same order of size as that noted on recatheterization. This indicates that during exercise the left to-right shunt in l/min in these patients was essentially unchanged, with a probably normal increase in the output of both the right and left ventricles. This is supported by the fact that the preoperative reduction of the saturation values in the pulmonary artery during exercise was very moderate compared with the result obtained on recatheterization, and also by the fact that preoperatively the right ventricular stroke volume decreased only negligibly during exercise.

Jonsson et al. (1957) found that the left to-right shunt in atrial septal defect decreased during exercise in 5 of 10 patients, but recently Davies and Gazetopoulos (1966) observed that in atrial septal defect with low pulmonary vascular resistance there were *parallel* increases in the systemic and pulmonary flow during exercise with little change in the magnitude of the left to-right shunt. This is in closer agreement to the present results, which also show this tendency on more strenuous exercise. In their series of 5 patients, Davies and Gazetopoulos had lower work loads throughout in their exercise tests, corresponding to an average oxygen consumption of 460 ml/min.

As in the larger present series of patients who underwent follow-up examination, a low cardiac output at rest, with a tendency to a hypokinetic circulation during exercise, was noted in this smaller group also In addition, the cardiac index in the systemic circulation

at rest was significantly lower preoperatively in the children (**) than at re-catheterization, but in the adults it was only slightly lower. Preoperatively however in consideration of the cardiac output in the pulmonary circulation the cardiac output in the systemic circulation increased to a probably normal extent during exercise. It may thus be assumed that, in these patients, even before the operation there was a tendency to hypokinetic systemic circulation with a low left ventricular output during exercise.

In order to compare the mechanical efficiency of the ventricles before and after the operation the ventricular work index and distensibility index were calculated. At rest, both these indices showed a significant reduction for the right ventricle on recatheterization. The different haemodynamic parameters which may be related to the left-to-right shunt in atrial septal defect have long been subjected to investigation. Rowe et al. (1961) who studied such parameters at rest, found that the only significant correlation was that between the size of the left-to-right shunt and the difference in distensibility index between the right and left ventricle. In Rowe's study however 4 out of 24 patients had pronounced pulmonary hypertension of the obstructive type, in three cases combined with a right-to-left shunt. In the present series there was no correlation between distensibility index and left-to-right shunt.

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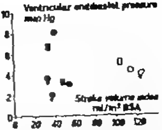

Fig. 23. Ventricular end-diastolic pressure (mm Hg) in relation to ventricular stroke volume index (ml/m² body surface area). Squares = children, circles = young adults and circles with cross = older adults. Open symbols = preoperative, and filled symbols = postoperative right ventricular stroke volume index. Crossed symbols = preoperative left ventricular stroke volume index.

capacity of the right ventricle to pump large volumes with a low filling pressure differs somewhat from the conditions in the left ventricle which (according to Starling's law) requires increasing filling pressures for increasing stroke volumes. When, in the present series, the end-diastolic pressure of the right ventricle is plotted against the stroke volume index of the right ventricle, the output of the right ventricle preoperatively is found to be large in relation to the end-diastolic pressure of the right ventricle, which lies at a normal level (Fig. 23). The preoperative end-diastolic pressure in the right ventricle was significantly higher (*) than at the follow-up examination, as also was the mean pressure in the right atrium. These pressures were probably sufficiently high to permit, in view of the distensibility and function curves of the ventricles, a large increase in filling of the right ventricle. The distensibility is determined mainly by the ventricular

wall thickness, which in turn is influenced by the systolic ventricular pressure and stroke volume. But like the mean pressure in the atrium, for technical reasons the end-diastolic ventricular pressure is also often difficult to determine and compare. Obviously this limits the value of the distensibility index in the present calculations. With this reservation the distensibility index for the right ventricle was determined in the present series, however and was found to be 25 on the average, preoperatively and 17 i.e. significantly lower (**) at the follow-up examination.

Depending on the degree and type of outflow obstruction in the right ventricle, the end-diastolic right ventricular pressure varies more than the pressure difference across the pulmonary vascular bed. Relatively accurate values can be obtained for the distensibility index for the left ventricle preoperatively whereas postoperatively the estimated values are only very approximate.

It seemed therefore more adequate to calculate the mechanical efficiency on the basis of the ventricular work index, which also can be determined more accurately during exercise. Postoperatively the right ventricular work index was significantly (***) lower and the left significantly (*) higher than preoperatively This may be an indication of satisfactory restitution of the ventricular function postoperatively despite the greatly increased load on the right ventricle before the operation.

In this series the pressures have also been reported with a view to comparing the pressure reaction during exercise before and after the operation. Preoperatively these pressures, with the exception of the PCV pressure, lay at the upper normal limit, and on recatheterization those in the right atrium and ventricle were significantly reduced (*) while the pulmonary arterial pressure was somewhat lower The PCV pressure remained essentially normal.

During exercise there was no significant difference between the preoperative values and those obtained on recatheterization for the pressures in the pulmonary artery The pressure reaction during exercise was normal in these patients on recatheterization and therefore the preoperative pressure reaction can also be regarded as normal in spite of the greatly augmented pulmonary blood flow at that time. A largely increased cardiac output in the pulmonary circulation at rest, with high normal pressures in the pulmonary artery and a low flow resistance across the pulmonary vascular bed thus allowed normal circulatory adaptation during exercise.

The pulmonary vascular resistance was somewhat higher throughout in the older than in the young patients both preoperatively and at the follow up examination, at rest and during exercise.

At recatheterization the pulmonary vascular resistance at rest was significantly higher in the children (**) and young adults (*) than preoperatively which is explained by the fact that after the operation the pressure reduction over the pulmonary vascular bed was usually considerably less pronounced than the decrease in the pulmonary blood flow In the older adults the pulmonary vascular resistance was found on recatheterization to be slightly higher but still at the

upper normal level, and in these patients the *postoperative* pressure reduction in the pulmonary artery was, on the average, somewhat more pronounced than in the children and young adults.

During exercise, however an abnormal reaction was noted in half of the patients, with increased pulmonary vascular resistance, but no relationship was found between this reaction and either the physical work capacity preoperative shunt or heart size.

The pressures in the brachial artery were normal both at rest and during exercise, with no difference between the preoperative values and those obtained on recatheterization. The systemic vascular resistance showed some reduction on recatheterization, but the values remained within the normal limits.

Summary

The results from haemodynamic investigations at rest and during exercise in 18 patients before and 11 months, on the average, after surgical repair of ASD sec are reported. One patient had pulmonary hypertension before the operation, but the values for the remaining patients did not deviate essentially from those reported for the whole series. Since the exercise tests were performed with the same work loads before as after operation, individual comparisons of the haemodynamic results could be made.

The heart rate and oxygen uptake were the same postoperatively as preoperatively both at rest and during exercise. An approximate evaluation of the magnitude of the left-to-right shunt during exercise was made by comparison between the pre- and postoperative flow conditions in the systemic and pulmonary circulations the shunt appeared to remain unchanged by exercise. A tendency to hypokinetic circulation was observed postoperatively and this was probably more pronounced before the operation.

The distensibility index for the right ventricle was significantly higher (**) preoperatively than postoperatively both at rest and during exercise at rest, this index was *significantly* higher (***) for the right than for the left ventricle, both pre and postoperatively.

A more accurate indication of the mechanical efficiency of the ventricles was the work index. This was significantly lower (***) postoperatively for the right ventricle, and this indicated satisfactory restitution of the ventricular function despite the preoperatively greatly increased work load for the ventricle.

The pressures at rest, pre- and postoperatively agreed with previously reported values for normal persons. The pulmonary vascular resistance values lay on the average, within the normal limits both at rest and during exercise, but preoperatively they were usually low and postoperatively somewhat higher. During exercise, however an abnormal increase of the pulmonary vascular resistance was noted in half of the patients. There was no relationship, however between this reaction and *either physical* work capacity preoperative shunt or heart size.

There was no statistically significant correlation either between the preoperative values of shunt index and heart volume or between their postoperative reductions.

wall thickness, which in turn is influenced by the systolic ventricular pressure and stroke volume. But, like the mean pressure in the atrium, for technical reasons the end-diastolic ventricular pressure is also often difficult to determine and compare. Obviously this limits the value of the distensibility index in the present calculations. With this reservation the distensibility index for the right ventricle was determined in the present series, however and was found to be 25 on the average, preoperatively and 17, i.e. significantly lower (**) at the follow up examination.

Depending on the degree and type of outflow obstruction in the right ventricle, the end-diastolic right ventricular pressure varies more than the pressure difference across the pulmonary vascular bed. Relatively accurate values can be obtained for the distensibility index for the left ventricle preoperatively whereas postoperatively the estimated values are only very approximate.

It seemed therefore more adequate to calculate the mechanical efficiency on the basis of the ventricular work index, which also can be determined more accurately during exercise. Postoperatively the right ventricular work index was significantly (***) lower and the left significantly (*) higher than preoperatively. This may be an indication of satisfactory restitution of the ventricular function postoperatively despite the greatly increased load on the right ventricle before the operation.

In this series the pressures have also been reported with a view to comparing the pressure reaction during exercise before and after the operation. Preoperatively these pressures, with the exception of the PCV pressure, lay at the upper normal limit, and on recatheterization those in the right atrium and ventricle were significantly reduced (*) while the pulmonary arterial pressure was somewhat lower The PCV pressure remained essentially normal.

During exercise there was no significant difference between the preoperative values and those obtained on recatheterization for the pressures in the pulmonary artery The pressure reaction during exercise was normal in these patients on recatheterization and therefore the preoperative pressure reaction can also be regarded as normal in spite of the greatly augmented pulmonary blood flow at that time. A largely increased cardiac output in the pulmonary circulation at rest, with high normal pressures in the pulmonary artery and a low flow resistance across the pulmonary vascular bed thus allowed normal circulatory adaptation during exercise.

The pulmonary vascular resistance was somewhat higher throughout in the older than in the young patients both preoperatively and at the follow-up examination, at rest and during exercise.

At recatheterization the pulmonary vascular resistance at rest was significantly higher in the children (**) and young adults (*) than preoperatively which is explained by the fact that after the operation the pressure reduction over the pulmonary vascular bed was usually considerably less pronounced than the decrease in the pulmonary blood flow In the older adults the pulmonary vascular resistance was found on recatheterization to be slightly higher but still at the

this investigation is hardly considered justifiable nowadays, since it has been found difficult to assess the position and size of the defect with certainty.

In the differential diagnosis between atrial septal defect of the secundum type (dorsal defect) and atrial septal defect of the primum type (ventral defect) the value of an angiocardiography is very limited owing, in particular, to the difficulty in determining with certainty the lower margin of the defect. Correct differentiation between these two types of defect is the deciding factor for the choice of operation method, since patients with a primum defect can only be operated on with the aid of extracorporeal circulation. The ECG pattern is the main guiding factor for this differential diagnosis (Toscano Barbosa et al. 1958, Arntzenius et al. 1963). In the present series extracorporeal circulation was used in four cases, where a primum defect could not be excluded. These patients showed the ECG pattern of the transitional, non-classic ASD sec type which can occur with a primum defect.

In spite of the perimyocardial disturbance in the postoperative stage, no signs of constrictive reaction were seen in this series at the follow-up examination, which may have been due to the fact that the pericardium was left open at the operation. The residual pathological T wave which became "normal" only during the exercise test, and was observed in 37 per cent of the cases, is difficult to assess from a prognostic aspect. In these patients, however, the myocardial metabolism during hypothermia and coronary perfusion is unknown. Up to the present, however, these T wave changes have not been found to be prognostically unfavourable, and should not give reason for an especially prolonged convalescence period for the patient in question.

The preoperatively low filling pressure in the left ventricle may explain the fact that a number of cases showed a low normal or reduced left ventricular output. These changes in the central circulation also resulted in a tendency to hypokinetic systemic circulation with reduced cardiac output in relation to oxygen uptake. Preoperatively the oxygen saturation in the superior vena cava was at a low normal level, but increased significantly (***) after the operation to a normal value. This may be an expression of a regulative mechanism with preoperatively increased peripheral utilization of the oxygen content.

In uncomplicated cases of ASD sec, closure of the defect restores the normal pressure conditions and creates the prerequisites for a normal central circulation. In spite of this, however, in a number of cases, especially children and older adults, a tendency to hypokinetic circulation was observed at the follow-up examination. In such cases controlled physical training, introduced gradually should be appropriate, and should improve the systemic circulation, and also, the psychological condition. This applies particularly to older patients, in whom a tendency to a long convalescence period probably has the directly opposite effect.

In uncomplicated cases of ASD sec the period of convalescence in adult patients should not necessarily be much longer than in children, and 6—8 weeks would seem sufficient.

General discussion and conclusions

The evaluation of the operation results in this series is based both on comparisons between preoperative and postoperative findings, where the patient serves as his own control and on comparisons of these values with known values from healthy normal subjects. In this way an idea is obtained of the *effect of the operation* The absence of a control series means, however that no opinion can be expressed with certainty as to the *prognosis without operation* since, as discussed in the introduction the variations in the natural history of the disease are wide.

In this series the indication for operation was a left to-right shunt of at least 30 % of the pulmonary blood flow With the low mortality figure and the low frequency of severe complications with the operation methods used here, it was justifiable to accept patients with small shunts also for operation.

The impression is obtained that the most suitable time for operation is at pre school or school age In this age group (age group A) both the duration of hospitalization and the convalescence period were considerably shorter than in adults. From social and psychological aspects, also, an operation is probably more easily acceptable in children, where the operation often is of a preventive nature The indication for operation in adults may on the other hand, be somewhat narrower but surgery should be advised with shunts of 50 % or more of the pulmonary blood flow

The physical cardiac findings both before and after operation were in agreement with those usually found in cases with ASD sec. In this series no relationship was found between the duration of the QRS complex and the degree of splitting of the second heart sound, either before or after operation, and therefore the residual pathologically split second sound, which was the most characteristic postoperative physical cardiac finding, can probably be explained by reduced elasticity in the pulmonary artery Preoperatively from the diagnostic point of view the splitting of the second heart sound and the diastolic filling murmur are the most important physical findings. Together with the typical ECG pattern and chest roentgenogram these findings, in most cases, form the basis for the final diagnosis in ASD sec. But the cardiological findings are not always typical and, furthermore, cannot usually provide any information about the presence or absence of anomalous venous return, so that up to now heart catheterization has been included in the clinical routine examination. In the present series the fact that the ASD sec was combined with partial anomalous pulmonary venous return in 19 per cent did not influence the choice of operation method but this is conceivable in isolated cases. In cases with partial anomalous pulmonary venous return an angiocardiography can give valuable information, while on the other hand in uncomplicated ASD sec

circulation disappears instantly after repair of an atrial septal defect. Normalization of heart sounds and murmurs, and also of the roentgenological heart volume takes place gradually. A faint systolic murmur was heard, however after the operation, probably caused by turbulent flow through the still dilated pulmonary artery. Reduced elasticity in the wall of the pulmonary artery may also explain the extensive splitting of the second heart sound after the operation while, compared with the preoperative conditions, the reduced flow volume may allow some physiological variation of the sound components.

In many cases of the present series there was some relationship between the size of the left-to-right shunt and the heart volume, but no significant correlation was found. A significant reduction was found in the roentgenological heart volume after the operation, however. On the other hand there was no statistically certain correlation between shunt reduction and reduction of heart volume.

On comparing the QRS pattern before and after operation it was found that this pattern in lead V remained unchanged, i.e. pathological, in about 50 % of the cases. Even though the *type* of QRS complex remained unchanged, however the *degree* of abnormality decreased. The amplitude reduction may correspond to regression of hypertrophy and/or dilatation in the right ventricular outflow tract. A residual pathological QRS pattern may point to a congenital abnormality in the right bundle branch, which will persist after surgery.

A pathological QRS complex in lead V_1 was not an expression of residual shunt.

At the follow-up examination a residual pathological T wave was found, and a *normalization* of this T wave during exercise was observed. The reason for this "status post myocardial lesion" reaction is discussed and is considered to be of no functional importance. This pathological T wave in the precordial leads at rest, though observed for a long period after the operation, should not be regarded as unfavourable.

Before the operation *the left-to-right* shunt in the entire series was, on the average, 61 % of the pulmonary *blood* flow.

At the *follow up examination* no residual shunts were found. The oxygen saturation in the superior vena cava lay at a normal level at the follow-up examination but was significantly higher than before the operation.

The postoperative pressure reaction in the pulmonary circulation, with reduction from preoperatively slightly raised or high normal pressure levels to normal values, was explained by the hyperkinetic *effect of the left to-right shunt*. Only in older adults was there a significant correlation between shunt size and systolic right ventricular pressure, but at the follow-up examination no correlation was found between pressure reduction and shunt.

On comparing the filling pressure of the ventricles before and after the operation it was found that, preoperatively *this* pressure was raised for the right ventricle and, in many cases, was lowered for the left. *This change* in the central circulation resulted in many cases in a low normal or reduced *left ventricular*

General summary

The main purpose of this investigation was to study the results of open heart surgery in atrial septal defects of the secundum type (ASD sec) The study was made on 107 patients, comprising a haemodynamically uncomplicated, uniform series of atrial septal defects of the secundum type, examined before and, on the average, 17 months after the operation.

Open repair was performed under hypothermia in 94 patients and with the aid of extracorporeal circulation in 13 patients. All patients were operated on by the same surgeon (V O Björk) The postoperative mortality was as low as 0.9 % and the total mortality 2.6 %

The clinical features and cardiological findings before and after operation were studied.

The ECG pattern before and after operation, the development of the ECG changes immediately after the operation and the ECG reaction during exercise tests at the follow up examination were analysed.

Haemodynamic studies were made by means of heart catheterization before the operation to estimate the significance and size of the left to-right shunt and at the follow up examination to prove that the defect was closed, but also for determination of circulatory dimensions at rest and during exercise for comparison with normal persons.

From a clinical aspect it was important to know not only that the defect was completely closed but, above all, the general cardiac condition of the patient after the operation.

The patients were divided into three age groups according to age at the time of operation, as follows A paediatric group of 50 patients below the age of 15 years, a group of 29 young adults of ages 15—29 years, and a group of 28 older adults of 30 years of age or older

The patients were also classified into function classes, and shunt and X ray groups.

The murmur was usually discovered at a routine examination during the pre-school or school period but was often rediscovered at a later examination. Only 5 out of 107 patients had sought medical advice for symptoms which could be related to cardiac disorder Preoperatively 44 patients had symptoms. The functional deterioration began after the age of 20 years.

After the operation almost all patients were symptom-free, but no significant change in the physical work capacity was found.

The physical findings before and after operation in this series were in agreement with previous findings in uncomplicated ASD sec. The excess volume load on the right heart and pulmonary

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output with a tendency to hypokinetic circulation. Preoperatively the oxygen saturation in the superior vena cava was at a low normal level and this may be an expression of a regulative mechanism with increased peripheral utilization of the oxygen content.

The circulatory efficiency i.e. the cardiac output in relation to oxygen uptake was analysed in a series of patients at the follow up examination. The results appeared to agree with the conditions in hypokinetic circulation. Children and older adults, especially showed low values for cardiac output both at rest and during exercise. This, in combination with a "high normal" pressure gradient across the pulmonary capillary bed gave rise to a somewhat high pulmonary vascular resistance.

In 18 patients individual comparisons of haemodynamic conditions before and after operation were made, both at rest and during exercise. An approximate evaluation of the magnitude of the left to-right shunt during exercise was made by comparison between the pre and postoperative flow conditions in the systemic and pulmonary circulation, and thus showed that the shunt appeared to remain unchanged by exercise. A tendency to hypokinetic systemic circulation was observed postoperatively and may have been more pronounced before the operation.

In uncomplicated cases of ASD sec, closure of the defect creates the prerequisites for a normal circulation. In patients with a tendency to hypokinetic circulation after the operation controlled physical training should improve the systemic circulation

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BY S ZOE WALSH, M D

ALMQVIST & WIKSELLS BOKTRYCKERI AB UPPSALA

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Cremer [1] is generally credited with being the first to obtain esophageal leads. Since then, a number of experimental and clinical studies in adults have appeared—including those of Lieberson & Lieberson [32], Brown [9], Helm et al. [26], Deglande & Laubry [19], Nyboer [35], Myers & Klein [34], Kistin et al [28], and Scherlis et al. [40]. However even in adults, normal values are based on relatively small numbers of healthy individuals. Not until 1932 was an analysis of such electrocardiograms in children reported by Bengtsson [5], who studied twenty healthy children aged 1 to 12 years and thirty two with various heart lesions. At about the same time, Franke [22] studied 9 infants with congenital heart disease. Then followed the investigations of Huth & Kollmann [27] and Ambaldi et al. [1], which were based on single examination of 10 and 30 healthy infants aged 1 month to 12 years and 7 days to 1 year respectively. Thus, although this approach permits recording of semidirect leads from the left atrium and is of acknowledged value in the study of arrhythmias, very little data is available in children and none in the neonate.

This report is based on the findings on serial examination of 100 healthy newborns during the first week of life. Normal standards and variations encountered are presented.

Leads V4R, V1 to V6, 2V1, 2V2 and V (the latter were recorded at the right and left second intercostal space and at the tip of the sternal xyphoid process).

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Method

One hundred healthy infants were studied on the first, second, third and fifth or sixth day of life. Four were not examined on the first day. Two infants had a birth weight of 2410 g and 2480 g respectively; the remainder weighed more than 2500 g each. All were the products of presumably uncomplicated deliveries without maternal analgesia or anesthesia, were cephalic presentations and had delayed clamping of the umbilical cord. There were no twins, no Caesarean sections, and no known maternal illness. Other data on these infants has been published elsewhere [47–51]

For purposes of determining differences with age, analysis was restricted to 68 infants, 43 of whom were female, who had had four examinations each. These infants were divided into 4 groups, with an average gestational age of 41 weeks each, based on age of initial examination.

Group I. 30 minutes old or less (17 infants).
Group II. 33 to 60 minutes old (21 infants).
Group III. 65 minutes to 4 hours old (13 infants).
Group IV. 4½ hours old (17 infants).

All recordings were taken at a paper speed of 100 mm/sec on a 4-channel jet recorder by the author with an assistant. Standard bipolar extremity, augmented unipolar extremity, 10 precordial[1] and a series of unipolar esophageal and gastric leads were obtained. The esophageal electrode was made by soldering a german silver bead measuring ~ mm in diameter to a 37 cm length of well-insulated copper

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wire This was then drawn through a 2 mm wide polyethylene tube marked at 1 cm intervals. The central terminal of Wilson was used as the indifferent electrode Systolic blood pressure was recorded with the Ashworth modification of the xylol recorder [2] and heart volume using Lysholm-Jonsell's modification of Röhrer Kahlstorf's method as described by Lind [33] was measured on roentgenograms of the chest on the first and fifth or sixth day of life

Rapid paper speed essential for the rapid heart rates of infancy a magnifying lens of ×5 simultaneous recording of standard leads periodic testing of paper speed and use of an external voltmeter increased the accuracy of measurements. Time intervals were estimated to the closest 5 msec and amplitudes to the closest 0 5 mm (05 mV) and corrected for standardization Measurements were made in accordance with the recommendations of the Criteria Committee of the New York Heart Association [18]

Every effort was made to disturb the infants as little as possible However the extremities were always gently pinioned down as previously described prior to taking any recordings. As infants invariably regurgitated and/or became restless when swallowing the electrode this approach was not used Instead, once the infant was sucking on a pacifier without using local anesthesia the oesophageal electrode was gradually advanced a distance of 23 cm via the nares. In the first 53 infants the catheter was withdrawn at 1 cm stages from 23 to 3 cm (21 leads) Because changes occurred with even minor displacement of the electrode especially in peri-atrial leads in the remaining 47 infants additional one-half cm levels were obtained between 18 and 8 cm (total 31 leads) Fluoroscopic control of electrode position was not deemed justified, but the electrode was held in place and great care was exercised in repeatedly checking the position at the nares.

Nomenclature and Treatment of Data

After all the measurements had been made the entire material was re-read to ensure uniformity of classification. No method seems exact and reproducible partly because minor displacement of the oesophageal electrode may go undetected In this study atrial leads have been strictly defined as only those in which the *P* wave has a sharp intrinsic deflection To minimize error no borderline cases have been included. Leads obtained above and below this level are supra- and infra atrial leads. The latter are further subdivided according to appearance of the ventricular complex, i e leads resembling one or more precordial leads and/or Lead II or aVF are ventricular and those neither resembling ventricular nor atrial leads are transitional With passage of the electrode, a characteristic series of patterns is seen, but exact points of reference cannot be used as pattern types overlap

Although all leads are included in the analysis measurements of amplitude of deflections and duration of intervals are confined to leads obtained at the following levels (*a*) highest (*h*) intermediate (*i*) and lowest (*l*) *atrial* (*b*) 1 and 3 cm *above the highest atrial* (supra-atrial leads (*a*) and (*b*)) (*c*) 1 and 3 cm below the lowest atrial and at approximately

2 cm stages distally (infra-atrial leads ( ) (b) (c), (d) and (e)) By using a set distance from atrial leads, serial diffe rences with age can be evaluated to some xtent and subsequent studies may more easily be compared to this data. On the other hand using a set distance from the nares results in a wide scatter of levels, g., 10 cm from the nares is found from 1 to 7 cm below the lowest atrial lead.

Statistical Methods

Where the number of cases decreases, this is either because no lead was available at the designated level or because the recording was unsatisfactory

The standard deviation was calculated with the following formula.

$$s.D. = \sqrt{\frac{n\sum x^2 - (\sum x)^2}{n(-1)}}$$

As the distribution of amplitudes of the *Qp Rp/Sp* ratio and ventricular *QRS* comple t nds to be skew percentiles ha e been determined in preference to means nd tandard deviations.

The first quartile is the value of the

$$\frac{+1\text{th}}{4}$$

of the cases when they are arrayed from lowest to highest the median, the

$$\frac{+1\text{th}}{}$$

and the third quartile the

$$\frac{3(+1)\text{th}}{4}$$

case

Differences were investigated between the 4 groups of infants using the standard tests (student s t test, chi square) Where there were no differences, the groups were combined for investigation of differences between 2 groups or of the whole group at different ages.

Anatomy

In the newborn, the esophagus starts as the continuation of the pharynx at the cricoid cartilage opposite the body of the 4th cervical vertebra, extends a distance of about 9 or 10 cm and termina tes at the cardiac orifice of the stomach level with the 9th or 10th dorsal vertebra [12 42]. It is 4 to 5 mm wide (empty) and the cardia is stated to be located bout 17 cm from the teeth [4]. According to Caffey the normal adult curves (upper and lower third—slightly convex to left mid portion—convex to right) and constrictions (origin, aortic arch crossing of left bronchus and at diaphragm) are present during infancy but less well defined.

The esophagus lies in close proximity to the left atrium, and for this reason provides a simple method for recording of atrial complexes of higher amplitudes than with more remote leads. In adults, there has been some discussion as to whether the lower end of the esophagus is solely in relation w th the posterior basal wall of the left ventricle. Some believe that slight changes in cardiac position of the heart may bring the interventri cular sulcus or even the right ventricle into relation with the esophagus [28]; others, that the diaphragmatic segment may often be in closer contact with the

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2 cm stages distally (infra-atrial leads (a) (b) (c), (d) and (e)). By using a set distance from atrial leads, serial differences with age can be evaluated to some extent and subsequent studies may more easily be compared to this data. On the other hand, using a set distance from the nares results in a wide scatter of levels, e.g. 19 cm from the nares is found from 1 to 7 cm below the lowest atrial lead.

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$$\frac{3(\quad 1)\text{th}}{4}$$

case

Differences were investigated between the 4 groups of infants using the standard tests (student s t test, chi square) Where there were no differences, the groups were combined for investigation of differences between 2 groups or of the whole group at different ages.

Anatomy

In the newborn, the esophagus starts as the continuation of the pharynx at the cricoid cartilage opposite the body of the 4th cervical vertebra, extends a distance of about 9 or 10 cm and termina tes at the cardiac orifice of the stomach, level w th the 9th or 10th dorsal vertebra [12 42]. It is 4 to 5 mm wide (empty) and the cardia is stated to be located about 17 cm from the teeth [4] According to Caffey the normal adult curves (upper and lower third—slightly convex to left mid portion—convex to right) and constrictions (origin, aortic arch crossing of left bronchus and at diaphragm) are present during infancy but less well defined.

The esophagus lies in close proximity to the left atrium, and for this reason, provides a simple method for recording of atrial complexes of higher amplitudes than with more remote leads. In adults, there has been some discussion as to whether the lower end of the esophagus is solely in relation with the posterior basal wall of the left ventricle. Some believe that slight changes in cardiac position of the heart may bring the interventricular sulcus or even the right ventricle into relation with the esophagus [28]; others, that the diaphragmatic segment may often be in closer contact with the

inferior vena cava or the posterior caudad segment of the right atrium [29] still others that neither of these chambers are in contiguity with the esophagus [10]. However in newborns, the posterior part of the inferior or diaphragmatic surface of the heart is stated to be formed solely by the atrial portion of the heart [38]

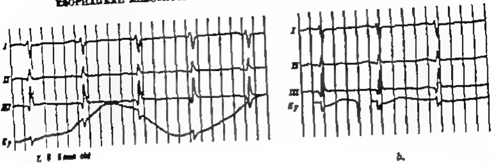
Artefacts

It seems fair to state that the number of artefacts or errors in labelling of esophageal leads exceed those encountered with routine electrocardiographic leads. This is not to say that many records cannot be obtained which are essentially artefact-free However in certain regions of the esophagus, notably near the atrium minimal displacement of the electrode may result in significant changes in the appearance of the complex Repeated careful checking of location, with an assistant holding the electrode exactly in place reduces this problem somewhat On the other hand when the electrode is in the upper esophagus, infants are often able to extrude the catheter with a forced expiration making its exact location in this region difficult to determine Although the location of the esophageal electrode was not determined by fluoroscopy it seems unlikely that curling of the catheter occurred because (1) the typical progression of complexes on withdrawal of the electrode was observed in every infant (2) there is a direct correlation ($r = 0.413$ $p < 0.001$) between the level of the transitional lead and the infant's length and (3) the catheter though flexible does not have a tendency to curl However in a few cases described by Kistin *et al.* [28] roentgenograms show the esophageal tube to be doubled up in the esophagus

The most common artefacts are baseline wandering *A–C* interference and variable amplitude. The incidence of a wandering baseline in various leads was not determined but was seen in most leads at some time This artefact can be reduced though not eliminated, by having the infant lie as quietly as possible. Both deep respirations and sucking seem to be mainly responsible for this finding but in some instances both may be present with a level baseline Sucking effects are probably greater in higher esophageal leads they are more irregular and cause sharp dips while deep respirations are regular and wavy and more common near the diaphragm (Fig 1) *A–C* interference is not uncommon in gastric and low esophageal leads, especially after feeding and is probably induced by contact with gastric contents. Slight withdrawal of the electrode improves the recording

Variations in amplitude of the *P* and *QRS* deflections are fairly common and also appear to be related to respirations. Such variations occur even in the absence of a wandering baseline and often affect the *P* wave more than the ventricular *QRS* complex

According to Brown, all electrodes and especially small metal ones are subject to polarization effects. Such effects become significant only when they are large which is uncommon. Then measurements of intervals are little affected but significant alterations in amplitude occur especially in the returning stroke from any sharply developed peak. These effects



a. b.

Fig. 1 Artefacts recorded with an esophageal lead 7 cm from the nares in 5-minute-old infant. (a) deep respirations—very regular baseline; (b) sucking—sudden disappearance of baseline. (Paper speed 100 mm/sec; distance between vertical time lines = 50 msec; tracing redrawn to scale.)

were not investigated, but as Brown states that they are rare it seems unlikely that they are of significance in the present study.

Artefacts are probably more frequent in adults. These have been variously ascribed to peristalsis, respirations, swallowing, poor contact, motion of the heart [28], transmitted pulsations from the aorta [30], and diaphragmatic contractions [19]. In this investigation, no constant artefact was observed from peristalsis, nor could movements of the heart or from transmitted pulsations be recognized.

Levels

Supra-atrial leads 1 and 3 cm above the highest atrial leads, as well as highest and intermediate atrial leads, are recorded at a mean of 10, 12, 13, and 14 cm from the nares. These levels do not change with age. On the other hand, lowest atrial and infra-atrial leads are initially recorded at mean levels of 15, 15.5, 17.5, 19, 21 and 23 cm from the nares, but at the end of the week are found at a slightly lower level, i.e., 15.5, 16.5, 18.5 and 19.5 cm respectively, little change having occurred in the lowest two leads. This shift with age is also present in transitional leads

TABLE 1 *Mean distance (cm) from the nares of esophageal leads on the first and fifth or sixth day of life.*

Groups combined as no significant differences present. Supra-atrial leads a and b are recorded 3 and 1 cm above the highest atrial lead. h, highest; i, intermediate; l, lowest atrial leads. Infra-atrial leads a, b, c, d, and e are recorded approximately 1, 3, 5, 7 and 9 cm below the lowest atrial lead.

	Supra-atrial		Atrial			Infra-atrial				
Day	a	b	h	i	l	a	b	c	d	e
1	9.94	11.94	12.63	13.70	14.97	15.63	17.56	19.33	1.30	23.00
5–6	10.07	12.07	13.04	14.17	15.[illegible]	16.40	18.40	19.92	21.71	23.00

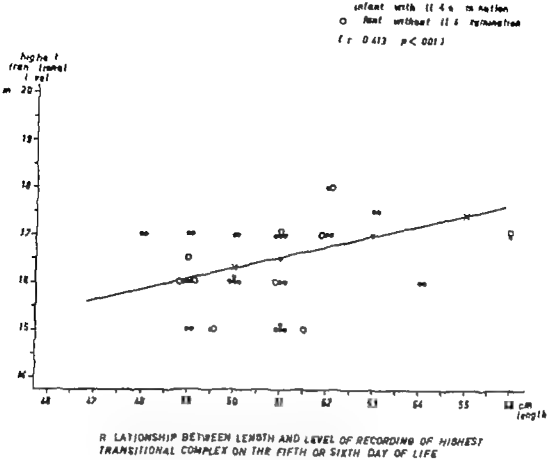


Fig — There is a direct relationship between the infant length and level of recording of the highest transitional complex. This is also true of mid-atrial and ventricular leads as defined in this study

which by definition are not dependent on location of atrial leads, suggesting that this is not a spurious finding (Table 1)

The mid atrial level varies directly with the length of the infant and histograms show a similar relationship between length and transitional and ventricular leads That is the longer the infant the lower the level of the respective lead (Fig 2) A similar trend between surface area and level of atrial recording is also present i e the greater the surface area the lower the level of the atrial leads However the area over which atrial leads are recorded in each infant is influenced not by length but by age In other words, these leads are inscribed over an area extending from a single point to 1 cm in 21 of 68 infants initially as compared to 5 of 68 infants at the end of the week and over an area from 2.5 to 4 0 cm in 18 infants initially as compared to 34 of 68 infants later The smaller the initial area from which atrial leads are obtained, the more likely the increase with age. Thus, increases occurred in 31 of 35 infants in whom atrial leads were obtained from an area of 1 5 cm or less initially in contrast to 12 of 34 infants with an area of 2 0 cm or more initially

As mentioned earlier the classification of atrial leads has been strictly based on presence of a sharp intrinsic deflection. This necessarily reduces the area from which atrial leads are obtained and affects the level of supra- and infra-atrial leads. The latter two regions are directly dependent on location of atrial leads, a possible source of error in serial studies. But the location of atrial leads, as shown above is dependent on the infant's age, length, surface area, as well as the direction of the P vector.

Heart Rate

The true resting heart rate is difficult to determine in the newborn because minimal stimuli may induce significant changes. Only continuous monitoring of heart rate in a sound proof room can be considered entirely satisfactory for this purpose. With this in mind, it is thought to be of interest to mention some of the findings encountered here because of the relatively long recording period, the attention paid to disturbing the infants as little as possible and the essentially physiological state of these infants at birth.

On the first day of life heart rate ranged from 74 to 200 with a mean of 123 beats/minute. There was little change in rate during the next few days, but at the end of the week the mean rate increased to 137 beats/minute.

Sinus arrhythmia was not uncommon especially after the first day of life and was not limited to infants with the slowest heart rates. Several infants had a transient wandering pacemaker in one or two leads, one of them also had a single atrial

Table 2. *Heart rate in esophageal leads showing mean, standard deviation and range in 68 healthy infants during the first week of life (groups combined).*

Day	1	2	3	5–6
m	123	127	123	137
S.D.	19.3	16.1	14.7	18.2
r^1	87–176	90–167	86–174	85–188
r^2	74–200	78–176	74–182	77–209
n	68	68	68	66
s.a.	5	13	16	17
w.p.	5*	2	6	1

* One of these infants also had a single atrial premature contraction.

r^1, range in atrial leads; r^2, range in other esophageal leads; s.a., sinus arrhythmia; w.p., wandering pacemaker.

premature contraction. (Table 2.) Still another infant, not included in the table developed a persistent wandering pacemaker on his last two examinations. Two other infants had complete right bundle-branch block and constant Wolff-Parkinson-White syndrome respectively on the first and second day of life (40). These findings were still present when they were reexamined at the age of one year.

It seems clear that mild arrhythmias are relatively common and that their presence cannot be adequately evaluated without considerably longer recording periods. As noted on page 30 brief shifts in pacemaker may be induced by the esophageal electrode itself.

On the first day of life rates are relatively rapid immediately after birth, become slower during the first hour and then gradually increase, but not to initial values. The increases at the end of the week have also been observed by Contis & Lind (15), but the mechanism for this change is not clear.

P Wave Duration

Measurements of the longest P wave duration P–R interval and heart rate were generally made in high or mid-atrial leads with a Qp wave and in lead V_2. Absence of the Qp wave is more commonly associated with shorter P waves Exact measurement of P wave duration is hampered by slurring of the Qp and Sp waves. The former is common while the latter is less frequent

In most leads measurements of P and P–R intervals vary in each lead as well as with each complex This often amounts to 10 or 20 msec but can be significant as Caceres & Kelser [11] have shown. Furthermore in such a lead as V_2, accuracy of measurement of the P wave at least in the newborn seems highly questionable because of the frequency of a low notch often with an initial isoelectric portion. This is probably true of all leads *from the right precordium* Left chest leads may be more satisfactory for accurate measurement of P wave duration in this group but greater amplification is needed *In the absence of several si*multaneous leads it may be still more difficult or impossible to determine exact onset or termination of waves.

On the first day of life the duration of the P wave in esophageal leads is relatively shorter after birth reaches a maximum at 35 to 60 minutes and then gradually decreases *throughout* the rest of the day More specifically mean values increase from 60 to 69 ($p <$ 01) and then decrease to 63 and 59 msec in the 4 groups *respectively* Median values are almost identical The P–R interval also tends to be longer in Group II infants but is not

TABLE 3 *P duration (msec) in atrial leads showing mean standard error standard deviation and range.*

Day	Group	P Duration I	II	III	IV
1	m	60	69	63	59
	S.E.	1 46	2.56	1 39	0.34
	S.D	6 0	11 7	5 0	1 4
		55–70	45–90	50– 0(74)	35–90
	n	17	1	13	17
5–6	m	49	53	33	53
	S.E.	1 55	1 03	1 22	1 70
	S D	6 4	4.7	4 4	7 0
		40–60	45–60	45–60(44)	40(44)–63
	n	17	21	13	17

Figures in parentheses indicat minimum and maximum values in infants *without* all 4 examinations.

statistically significant By the second day mean values in all groups range from [illegible] to 60 msec and further decrease to 49–53 msec at the end of the week. (Table 3 4) Mean individual decreases *are greatest from the first to the second* day less from the second to the third, least from the third to the fifth or sixth day of life and most marked in infants *in Groups II and III*, those with the longest initial values. The findings are essentially similar in simultaneously recorded leads II and V Neither the changes in duration *of the P* wave on the first day of life nor during the week were found to be related to changes in heart rate Likewise significant decreases in duration of the P–R interval with age independent of changes in heart rate also occur and median values on the first and last examination are almost identical with the means

Scattergrams show a linear relationship between P wave duration in atrial leads and in lead II both on the first and the

TABLE 4 *Q–R_x time (msec) in highest, intermediate and lowest atrial leads and P R interval (msec) in atrial leads showing mean standard error standard deviation and range on the first and fifth or sixth day of life (groups combined)*

Da		Q–R_x time h	i	l	P–R interval
1	m	[illegible]	30	27	114
	s.e.	1 67	1 47	1.70	1 0
		10	11	9	14
		15–66	10–55	10–50	8[illegible]–180
		34	56	30	83
5–6	m	28	[illegible]	23	103
	s.	1.39	0.79	1 94	1 79
	D.	6	6	8	14
		15–40	10–33	10–48	70–180
		22	56	17	68

Figure in parentheses indicates maximum va lue in infant without all 4 examinations.

fifth or sixth day of life. A similar relationship between duration of the *P* wave in lead I and the esophageal lead is only present on the first day of life in infants one hour of age or less, but not subsequently No relationship could be demonstrated bet een the size of the largest intrinsic deflection and the dura tion of this interval.

On the first day of life 2 of 17 infants in Group I as compared to 8 of 17 infants in Group IV had a longer *P* wave duration in atrial leads than in lead II. At the end of the week, the distribution was similar for all 68 infants with no difference in the majority and an equal number of longer *P* w ves in either lead II or the atrial lead (not exceeding 30 msec but generally $< \pm 15$ msec).

Recordings of lead I and esophageal leads were not taken simultaneously but it was thought to be of interest to also compare *P* wave duration in these leads. In this case, on the first day of life, 12 of 17 infants (70 %) in Group I had longer *P* waves in atrial leads as compared to 5 of 17 infants (31 %) in Group IV At the end of the week, the distribution was similar for all 68 infants. 40 (59 %) had longer *P* waves in atrial leads, 17 (25 %) longer values in V_1, and no difference was present in the remain der

The difference in time of onset of the *P* wave in simultaneously recorded atrial esophageal leads, preferably with a *Qp* wave, and in lead II was determined. Correction was made for any difference in timing between the channels. Questionable cases were classified as no dif ference. Absence of a *Qp* wave was relatively uncommon but did not appear to influence the findings. On the first day of life, onset of the *P* wave was ear lier in the esophageal lead in 17 % of the infants in Group I as compared to 64 % of those in Group IV ($p < .05$). By the end of the week, the esophageal *P* wave was earlier in 23 (34 %) later in 15 (22 %) and there was no difference in the majority [30] (44 %) of infants. These results are in accord with the abovementioned differences in *P* wave duration in simultaneously recorded lead II and the esophageal lead.

In adults, Copeland and associates [16], using a paper speed of 25 mm/sec, found that the trial deflection in esophageal leads is of *significantly shorter* duration and of later onset *than in lead* II. In their opinion, an esophageal electrode located in the vicinity of atrial transition (equiphasic *P* wave) is insensitive to the initial and terminal forces

P Wave Duration

Measurements of the longest P wave duration, P–R interval and heart rate were generally made in high or mid-atrial leads with a Qp wave and in lead V_1. Absence of the Qp wave is more commonly associated with shorter P waves. Exact measurement of P wave duration is hampered by slurring of the Qp and Sp waves. The former is common while the latter is less frequent

In most leads measurements of P and P–R intervals vary in each lead as well as with each complex This often amounts to 10 or 20 msec, but can be significant as Caceres & Kelser [11] have shown. Furthermore in such a lead as V_1, accuracy of measurement of the P wave at least in the newborn seems highly questionable because of the frequency of a low notch often with an initial isoelectric portion *This is probably true of all leads* from the right precordium Left chest leads may be more satisfactory for accurate measurement of P wave duration in this group but greater amplification is needed. In the absence of several simultaneous leads, it may be still more difficult or impossible to determine exact onset or termination of waves.

On the first day of life the duration of the P wave in esophageal leads is relatively shorter after birth reaches a maximum at 35 to 60 minutes and then gradually decreases throughout the rest of the day More specifically mean values increase from 60 to 69 ($p < 01$) and then decrease to 63 and 59 msec in the 4 groups respectively Median values are almost identical The P–R interval also tends to be longer in Group II infants but is not

TABLE 3 *P duration (msec) in atrial leads showing mean standard error standard deviation and range.*

Day	Group	P Duration I	II	III	IV
1	m	60	69	63	59
	s.E.	1 46	2.56	1.39	0.34
	s.D	6.0	11 7	5.0	1 4
	r	55–70	43–90	50– 0[75]	35–90
	n	17	21	13	17
5–6	m	49	53	53	[illegible]
	s.E.	1.53	1 03	1 23	1 0
	s.D	6.4	4 7	4 4	7 0
		40–60	45–60	45–60[65]	40[35] –65
	n	17	21	13	17

Figures in parentheses indicat minimum and maximum values in infants without all 4 examinations.

statistically significant By the second day mean values in all groups range from 54 to 60 msec and further decrease to 40–53 msec at the end of the week. (Table 3 4.) *Mean individual decreases* are greatest from the first to the second day less from the second to the third, least from the third to the fifth or sixth day of life, and most marked in infants in Groups II and III those with the longest initial values. The findings are essentially similar in simultaneously recorded leads II and V Neither the changes in duration of the P wave on the first day of life nor during the week were found to be related to changes in heart rate Likewise significant decreases in duration of the P–R interval with age independent of changes in heart rate also occur and median values on the first and last examination are almost identical with the means.

Scattergrams show a linear relationship between P wave duration in atrial leads and in lead II both on the first and the

TABLE 4 *Q–R$_p$ time (msec) in highest intermediate and lowest atrial leads and P–R interval (msec) in atrial leads showing mean, standard error standard deviation and range on the first and fifth or sixth day of life (groups combined)*

Day		Q–R$_p$ time h	i	l	P–R interval
1	m.	33	30	37	114
	S.E.	1.67	1.47	1.76	1.70
	D	10	11	9	14
		15–60	10–55	10–60	85–160
		34	36	28	68
5–6	m.	28	24	23	102
	E.	1.33	0.79	1.04	1.70
	D.	6	6	8	14
		15–40	10–35	15–45	70–150
		22	58	17	68

Figure in parentheses indicates minimum value in infant without all 4 examinations.

fifth or sixth day of life. A similar relationship between duration of the P wave in lead V and the esophageal lead is only present on the first day of life in infants one hour of age or less, but not subsequently. No relationship could be demonstrated between the size of the largest intrinsic deflection and the duration of this interval.

On the first day of life 2 of 17 infants in Group I as compared to 8 of 17 infants in Group IV had a longer P wave duration in atrial leads than in lead II. At the end of the week, the distribution was similar for all 68 infants with no difference in the majority and an equal number of longer P waves in either lead II or the atrial lead (not exceeding 30 msec, but generally $\leq \pm 15$ msec).

Recordings of lead V and esophageal leads were not taken simultaneously but it was thought to be of interest to also compare P wave duration in these leads. In this case on the first day of life 12 of 17 infants (70%) in Group I had longer P waves in atrial leads as compared to 5 of 17 infants (31%) in Group IV. At the end of the week, the distribution was similar for all 68 infants. 40 (59%) had longer P waves in atrial leads, 17 (25%) longer values in V_{1}, and no difference was present in the remainder.

The difference in time of onset of the P wave in simultaneously recorded atrial esophageal leads, preferably with a Qp wave and in lead II was determined. Correction was made for any difference in timing between the channels. Questionable cases were classified as no difference. Absence of a Qp wave was relatively uncommon but did not appear to influence the findings. On the first day of life, onset of the P wave was earlier in the esophageal lead in 17% of the infants in Group I as compared to 64% of those in Group IV ($p < 0.05$). By the end of the week, the esophageal P wave was earlier in 23 (34%) later in 15 (22%) and there was no difference in the majority [30] (44%) of infants. These results are in accord with the abovementioned differences in P wave duration in simultaneously recorded lead II and the esophageal lead.

In adults, Copeland and associates [16], using a paper speed of 25 mm/sec, found that the atrial deflection in esophageal leads is of significantly shorter duration and of later onset than in lead II. In their opinion, an esophageal electrode located in the vicinity of atrial transition (equiphasic P wave) is insensitive to the initial and terminal forces

P Wave Duration

Measurements of the longest P wave duration, P–R interval and heart rate were generally made in high or mid-atrial leads with a Qp wave and in lead V. Absence of the Qp wave is more commonly associated with shorter P waves. Exact measurement of P wave duration is hampered by slurring of the Qp and Sp waves. The former is common while the latter is less frequent.

In most leads, measurements of P and P–R intervals vary in each lead as well as with each complex. This often amounts to 10 or 20 msec but can be significant, as Caceres & Kelser [11] have shown. Furthermore in such a lead as V_1, accuracy of measurement of the P wave at least in the newborn, seems highly questionable because of the frequency of a low notch often with an initial isoelectric portion. This is probably true of all leads from the right precordium. Left chest leads may be more satisfactory for accurate measurement of P wave duration in this group but greater amplification is needed. In the absence of several simultaneous leads it may be still more difficult or impossible to determine exact onset or termination of waves.

On the first day of life, the duration of the P wave in esophageal leads is relatively shorter after birth, reaches a maximum at 30 to 60 minutes and then gradually decreases throughout the rest of the day. More specifically mean values increase from 60 to 69 ($p < 01$) and then decrease to 63 and 59 msec in the 4 groups respectively. Median values are almost identical. The P–R interval also tends to be longer in Group II infants but is not statistically significant. By the second day mean values in all groups range from 54 to 60 msec and further decrease to 40–53 msec at the end of the week. (Table 3, 4.) Mean individual decreases are greatest from the first to the second day, less from the second to the third, least from the third to the fifth or sixth day of life and most marked in infants in Groups II and III, those with the longest initial values. The findings are essentially similar in simultaneously recorded leads II and V_1. Neither the changes in duration of the P wave on the first day of life nor during the week were found to be related to changes in heart rate. Likewise significant decreases in duration of the P–R interval with age independent of changes in heart rate also occur and median values on the first and last examination are almost identical with the means.

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	s.e.	1 46	2.56	1.39	0.34
	s.d	6 0	11 7	5.0	1 4
		55–70	45–90	50– 0(70)	35–90
	n	17	21	13	17
5–6	m	49	53	53	33
	s.e.	1 65	1 03	1.22	1 70
	s.d	6.4	4 7	4.5	7 0
	r	40–60	45–60	45–60(40)	40(34) –65
	n	17	21	13	17

Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

TABLE 4. *Q–R_p time (msec) in highest intermediate and lowest atrial leads and P R interval (msec) in atrial leads showing mean standard error standard deviation and range on the first and fifth or sixth day of life (groups combined)*

Day		Q–R_p time h	i	l	P R interval
1	m	24	20	17	114
	s.e.	1.67	1.47	1.[illegible]	1.70
	s.d.	10	11	9	14
		15–40	10–55	10–30	[illegible]–150
		38	36	26	63
5–6	m	26	24	23	108
	s.e.	1.22	0.79	1.04	1.70
	s.d.	6	6	8	14
		15–40	10–33	15–45	70–160
		22	56	17	68

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On the first day of life the duration of the P wave in esophageal leads is relatively shorter after birth reaches a maximum at 35 to 60 minutes and then gradually decreases throughout the rest of the day More specifically mean values increase from 60 to 60 ($p <$ 01) and then decrease to 63 and 50 msec in the 4 groups respectively Median values are almost identical The P–R interval also tends to be longer in Group II infants but is not

Table 3 *P duration (msec) in atrial leads showing mean standard error standard deviation and range.*

Day	Group	P Duration I	II	III	IV
1	m	60	60	63	59
	s.E.	1 46	2.56	1 19	0 34
	s.D	6 0	11 7	5.0	1 4
		55–70	45–90	50– 0(74)	35–90
	n	17	1	[illegible]	17
5–6	m	49	53	53	33
	s.E.	1 55	1 03	1 23	1 0
	s.D	6 4	4 7	4.4	7 0
		40–60	45–60	43–60(55)	40(33)–63
	n	17	21	13	17

Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

statistically significant. By the second day mean values in all groups range from 54 to 60 msec and further decrease to 40–53 msec at the end of the week (Table 3 4) Mean individual decreases are greatest from the first to the second day less from the second to the third least from the third to the fifth or sixth day of life and most marked in infants in Groups II and III those with the longest initial values. The findings are essentially similar in simultaneously recorded leads II and V_1. Neither the changes in duration of the P wave on the first day of life nor during the week were found to be related to changes in heart rate Likewise significant decreases in duration of the P–R interval with age independent of changes in heart rate also occur and median values on the first and last examination are almost identical with the means

Scattergrams show a linear relationship between P wave duration in atrial leads and in lead II both on the first and the

TABLE 4. *Q–R, time (msec) in highest, intermediate and lowest atrial leads and P–R interval (msec) in atrial leads showing mean, standard error, standard deviation and range on the first and fifth or sixth day of life (groups combined).*

Day		Q–R time h	Q–R time i	Q–R time l	P–R interval
1	m.	23	30	27	114
	s.e.	1.67	1.47	1.76	1.70
	s.d.	[illegible]	11	9	14
		15–60	10–45	10–60	65(?) 160
		36	30	28	68
5–6	m.	28	[illegible]	23	103
	s.e.	1.28	0.70	1.04	1.70
	s.d.	4	6	8	14
		15–40	10–25	15–45	70–150
	n.	22	48	17	68

Figure in parentheses indicates maximum value in infant without all 4 examinations.

fifth or sixth day of life. A similar relationship between duration of the P wave in lead V and the esophageal lead is only present on the first day of life in infants one hour of age or less, but not subsequently. No relationship could be demonstrated between the size of the largest intrinsic deflection and the duration of this interval.

On the first day of life, 2 of 17 infants in Group I as compared to 8 of 17 infants in Group IV had a longer P wave duration in atrial leads than in lead II. At the end of the week, the distribution was similar for all 68 infants with no difference in the majority and an equal number of longer P waves in either lead II or the atrial lead (not exceeding 30 msec but generally ≤ ± 15 msec).

Recordings of lead V and esophageal leads were not taken simultaneously but it was thought to be of interest to also compare P wave duration in these leads. In this case, on the first day of life, 12 of 17 infants (70%) in Group I had longer P waves in atrial leads as compared to 5 of 17 infants (31%) in Group IV. At the end of the week the distribution was similar for all 68 infants: 40 (59%) had longer P waves in atrial leads, 17 (25%) longer values in V_1, and no difference was present in the remainder.

The difference in time of onset of the P wave in simultaneously recorded atrial esophageal leads, preferably with a Qp wave and in lead II was determined. Correction was made for any difference in timing between the channels. Questionable cases were classified as no difference. Absence of a Qp wave was relatively uncommon but did not appear to influence the findings. On the first day of life, onset of the P wave was earlier in the esophageal lead in 17% of the infants in Group I as compared to 64% of those in Group IV ($p < .05$). By the end of the week, the esophageal P wave was earlier in 23 (34%), later in 15 (22%) and there was no difference in the majority [30] (44%) of infants. These results are in accord with the abovementioned differences in P wave duration in simultaneously recorded lead II and the esophageal lead.

In adults Copeland and associates [16] using a paper speed of 25 mm/sec, found that the atrial deflection in esophageal leads is of significantly shorter duration and of later onset than in lead II. In their opinion, an esophageal electrode located in the vicinity of atrial transition (equiphasic P wave) is insensitive to the initial and terminal forces

of atrial depolarization According to Brown P wave duration in esophageal electrocardiograms is usually longer than that in conventional leads But he includes initial positive and late negative waves which in this study were often not considered to be a true part of the P wave He also mentions that a small wave may precede onset of the P wave in lead II

Q Rp Time

The Q–Rp time in atrial leads is measured from the take-off of the Qp to the peak of the Rp wave The duration of this interval varies at different levels but tends to be greater in higher leads also noted by Brown On the first day of life mean values were longer in highest atrial leads and tended to be longer at all three levels in infants in Groups II and III although the latter difference was not statistically significant As in the case of P wave duration significant decreases also occur during the first week of life ($p < 001$) unrelated to changes in heart rate That is on the first day of life at the intermediate atrial level 18 of 56 infants have an interval of 40 msec or more as compared to none of 58 infants at the end of the week (Table 4)

Using scattergrams, the duration of this interval was not found to be related to the size of the largest intrinsic deflection heart volume nor the level of the systolic blood pressure A direct linear relationship between P wave duration and the Q–Rp interval in the intermediate atrial lead is present in all groups only on the first day of life Subsequently there is only a tendency to such a relationship in infants in Groups III and IV

P Wave Amplitude[1]

When the electrode is placed in the stomach and withdrawn, the contour direction and amplitude of the P wave gradually change as the atrial level is approached. The P wave—initially small round and positive—increases in amplitude becomes diphasic, and often of considerable magnitude with or without an initial Qp and then low round and negative of gradually decreasing amplitude The exact site of these changes varies, but tends to begin abruptly at the atrial level. As mentioned earlier variations in amplitude are not uncommon and are presumably respiratory

In some cases, the P wave remains negative even below the atrium In others, the intrinsic deflection is of such low amplitude as to interfere with exact determination of the atrial level or else as is commonly found, it becomes isoelectric in the lowest atrial leads or slightly below this point. Such low amplitude P waves have also been observed in adults by Brown who attributes them in part to electrical events occurring in the neighboring inferior vena cava.

An initial sloping positive wave not uncommonly precedes the Qp wave Occasionally it has a sharper contour and seems to be part of the atrial P wave More often it is inscribed with termination of the T wave or the latter half of the U wave in simultaneously recorded standard bi polar leads. Just below the atrial level, instead of a Qp wave, an initial

[1] QSp waves are listed with the Sp wave in supra-atrial and highest atrial leads.

Table 5. Q amplitude in 1/10 mV in atrial leads showing quartiles and range during the first week of life.

		b		*c*		*d*	
Day	Group	I + II	III + IV	I + II	III + IV	I + II	III + IV
1	25 %	0.5	0.5	0.5	0.5	0.5	0.4
	50 %	0.5	1.0	0.5	1.0	0.5	1.0
	75 %	1.0	1.0	1.0	1.5	0.5	1.4
		0.5–1.5	0.5–1.5	0.5–1.5	0.5–1.6	0.5	0.5–1.5
	n	34	28	38	30	34	21
	No. waves	16	16	16	11	30	17
5–8	25 %	0.5	0.5	0.5	0.5	0.5	0.5
	50 %	0.5	1.0	0.5	1.0	0.5	0.5
	75 %	1.5	1.0	1.0	1.0	1.0	0.9
		0.5–1.5	0.5–1.0	0.5–2.0	0.5–2.0	0.5–1.0	0.5–1.0
	n	30	29	30	30	37	30
	No. waves	27	23	14	4	31	26

Cases with *Qp* wa of 0.5 mm or more.

small positive wave more like a notch on the upstroke of the *Rp* may be seen. This wave may interfere with measurement of *P* wave amplitude.

The *Qp* wave is often slurred, but can vary from slurred to sharp even in the same lead—a possible respiratory effect—thereby causing considerable difficulty in measurement of duration of the atrial *P* wave. This wave is of greatest amplitude at or slightly above the atrial level. It never exceeds 0.25 mV and may be seen only as an early notch on a broad peaked negative wave. In a few cases, it is more prominent in the mid-atrium, and may not be present in leads above this. On the first day of life, the differences between medians of younger and older infants, i.e. those older than one hour of age are just short of significant at highest and lowest atrial levels. In lowest atrial leads, a *Qp* wave is present in only *one-fifth of the infants*. (Table 5).

At birth, the mean amplitude of the Rp wave in intra-atrial lead (d) is slightly lower in infants in Groups I and II (just short of significant). However increases in most leads, apart from the highest *atrial lead, are greater in younger infants* from the first to the last examination but only of *statistical significance in lowest* atrial and intra-atrial leads (*c*) and (*d*). About one-third of the infants at birth and at the end of the week have an *Rp* in highest atrial leads while only seven of them did not have this wave at some time during the first week of life in intermediate atrial leads. High amplitudes are common with a maximum of 1.2 mV on the first day and of 0.9 mV at the end of the week. Although the highest values of the *Rp* wave are recorded at the latter level, relatively large amplitudes are also seen in lowest atrial leads. As the distribution of values was skew for *Rp* in highest atrial and *Sp* in lowest atrial leads, medians were also calculated, but no significant differences were noted.

Significantly lower mean values of the *Sp* wave are recorded *initially* in

TABLE 6A R_p and S_p amplitudes in 1/10 mV in esophageal leads showing range mean and standard deviation during the first week of life.

	Supra-atrial				Atrial											
			b^1		h								l			
			s			r					s		r	r		
p	I + II	III + IV	I + II	III + IV	I + II	III + IV	I + II	III + IV	I + I	III + IV	I + II	III + IV	I + II	III + IV	I + II	III + IV
1																
	0 9	0 93	1.80	2.17	0 41	0 48	3 46	4 16	3 24	3 30	3.41	4 13	3.88	2 93	0 79	1 76
D	0.41	0 43	0 64	0 68	0 62	0 74	1.20	1.28	1 51	2.73	1 69	2.57	1 48	2.10	0 78	1 76
	0 5–2.0	0 5–2.0	1 0–3.0	1 0–3.5	0.5–2.0	0.5–2.5	1 0–6.5	2.0–7 0	1 0–7.5	0.5–12.5	1 0–8.5	1 0–10.5 (13.0)	0.5–9.0	0.5–8.5	0.5–2.5	0.5–7.5
	38	30	38	30	34	28	34	28	38	30	38	30	34	21	34	21
zeros	0	1	0	0	22	17	0	0	1	0	0	0	0	0	[illegible]	1
2																
	1 04	0 88	2.33	2.12	0 24	0 28	3.94	4.30	2.80	3 09	3.12	3.63	2.88	2.94	0 86	1.56
D	0 42	0 42	1 01	0 70	0 43	0.80	1 70	2.01	1 88	2.0*	1 56	2.65	1 58	1 60	1.00	[illegible]
	0 5–2.5	0 5–1.5	1 0–5 0 (0 5)	1 0–4 0 (0 5)	0.5–3 5	0.5–3.5	1 0–9 0	1 0–10 0	0.5–8.0	1 0–9 0	0.5–7 5	1 0–14.5 (0)	0.5–6.5	0.5–6.5	0.5–3.0	0.5–6.0
	38	30	38	30	35	30	[illegible]	30	38	28	38	7	[illegible]	25	33	25
zeros	0	2	0	0	28	21	0	0	1	0	0	0	1		13	2
3																
	1.27	1 10	2.43	2.53	0 11	0.38	4 40	5 02	3.21	3.10	3.72	4 00	3.51	2.98	0 84	1.35
D	0.54	0 47	0 90	0 97	0.33	0 90	1 73	2.37	1 76	1 78	1 94	3.23	2.12	1 77	0 66	1 19
	0 5–2.5	0.5–2.0	1 0–4.5	1 0–4.0 (0.5)	0.5–1 5	0.5–4 0	1.5–10 0	2.0–12.0 (0.5)	0 5–8.5	0.5–6 0 (0.5)	0 5–8.5	0.5–17 0 (0)	0.5–12.0	0 5–7 0	0.5–3.0	(5.5) 0.5–4 0
	37	30	38	30	[illegible]	20	37	29	38	30	38	30	37	27	37	27
zeros	0	1	0	0	22	23	0	0	2	1	0	0	1	1	15	7
5–6																
	1.24	1 05	2 71	2.42	0 34	0 21	4.36	3.88	3.55	3.28	3.03	3 63	3 35	3 07	1 12	1 40
D	0.50	0.51	0 77	0 97 (0)	0.55	0 41 (3.5)	1 40	1 20 (10 0)	2.01	1 70 (11 0)	1 71	2.44 (0)	1 07	1 94	1 07	[illegible]
	0.5–2.5	0 5–2.5	1 0–4 0	1 0–6 0	0.5–2.0	0 5–2.0	2.0–9 0	1 5–7 5	0.5–9 0	1 0–8 0	1 0–8 0	0.5–13.0	1 0–8 0	0 5–8 0	0.5–4.5	0 5–4 0
	38	30	38	30	38	20	38	20	38	30	38	30	37	30	[illegible]	30
zeros	0	1	0	0	25	23	0	0	0	1	0	0	0	[illegible]	12	5
p	0 01		< 0 001				< 0 001						< 0 05			

μs wa 'rs are included.

Infra atrial

b d

Group I II III IV I II III IV I II III IV I II III IV I II III IV I II III IV

Group												
Day 1 No. zeros m s.d. n	1 2.24 1.31 0.5–5.0 37	0 2.10 1.14 0.5–5.0 [illegible]	1	1	0 1.14 0.63 0.5–2.5 [illegible]	0 1.21 0.51 0.5–2.5 28	2 0.88 0.41 0.5–1.5 37	3 0.83 0.46 0.5–2.0 29	3 0.73 0.30 0.5–1.5 37	1 0.90 0.42 ([illegible]) 0.5–2.0 26	0 0.83 0.34 0.5–1.5 31	0 0.93 0.44 0.5–2.0 20
Day 2 m s.d. n No. zeros	2.01 1.26 0.5–5.0 28 0	2.26 0.91 (0.5) 1.0–4.5 27 0	0	2	1.09 0.66 0.5–3.0 28 2	1.25 0.59 0.5–2.5 30 1	0.80 0.38 0.5–1.5 [illegible] 1	0.93 0.43 (3.0) 0.5–1.5 29 1	0.79 0.41 0.5–3.0 26 2	0.73 0.32 (2.0) 0.5–1.5 26 0	0.60 0.36 0.5–1.5 22 1	0.76 0.30 0.5–1.5 19 0
Day 3 m s. n No. zeros	2.22 1.23 0.5–6.0 31 0	2.20 1.19 0.5–5.0 28 0	0	2	1.15 0.49 0.5–2.0 [illegible] 0	1.12 0.54 0.5–2.5 28 1	1.14 0.41 0.5–2.0 37 0	0.98 0.38 (2.5) 0.5–1.5 28 0	0.93 0.40 0.5–2.0 26 0	0.84 0.30 0.5–2.0 27 1	1.05 0.45 0.5–2.5 22 0	0.58 0.82 0.5–1.5 28 1
Days 5–6 m s. n No. zeros p	2.27 1.11 0.5–5.0 37 0	2.14 1.22 1.0–5.0 28 2	0	0	1.27 0.76 0.5–2.5 28 0 < 0.05	1.27 0.52 1.0–3.0 30 1	1.27 0.40 0.5–2.5 37 0 < 0.001	1.10 0.42 0.5–2.0 29 1 < 0.05	1.07 0.40 0.5–2.0 30 0 < 0.001	0.98 0.40 ([illegible]) 0.5–1.5 26 1	1.02 0.45 0.5–2.0 [illegible] 0	0.88 0.28 0.5–1.5 14 0

p Refers to significant differences from day 1 to 5–6.
Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

TABLE 6A R_s and S_s amplitudes in 1/10 mV in esophageal leads showing range mean and standard deviation during the first week of life

	Supra-atrial				Atrial											
			b^1		h				e				l			
...up	I + II [s]	III + IV [s]	I + II	III + IV	I + II	III + IV	I + II [s]	III + IV	I + I [r]	III + IV	I + II	III + IV	I + II	III + IV	I + II [s]	III + IV [s]
...y 1																
...	0.65	0.95	1.80	2.17	0.41	0.48	3.46	4.10	3.24	3.30	3.41	4.13	2.88	2.93	0.70	1.76
...D	0.41	0.43	0.64	0.66	0.62	0.74	1.26	1.28	1.51	2.73	1.89	2.57	1.48	2.16	0.78	1.76
	0.5–2.0	0.5–2.0	1.0–2.0	1.0–3.5	0.5–2.0	0.5–2.5	1.0–6.5	2.0–7.0	1.0–7.5	0.5–12.5	1.0–8.5	1.0–10.5 (13.0)	0.5–6.0	0.5–8.5	0.5–2.5	0.5–7....
	38	30	38	30	34	28	34	28	38	30	38	30	34	21	34	21
... zeros	0	1	0	0	22	17	0	0	1	0	0	0	0	0	12	1
...y 2																
...	1.04	0.88	2.33	2.12	0.24	0.38	2.94	4.30	2.80	3.09	3.12	3.63	2.88	2.94	0.86	1.56
...D	0.42	0.42	1.01	0.70	0.43	0.80	1.78	2.01	1.66	2.0*	1.56	2.05	1.58	1.60	1.00	1.42
	0.5–2.5	0.5–1.5	1.0–5.0 (0.5)	1.0–4.0 (0.5)	0.5–2.5	0.5–3.5	1.0–9.0	1.0–10.0	0.5–8.0	1.0–9.0	0.5–7.5	1.0–14.5 (0)	0.5–6.5	0.5–6.5	0.5–3.0	0.5–6...
	38	30	38	30	35	30	35	30	38	28	36	27	34	25	33	25
... zeros	0	2	0	0	28	[illegible]	0	0	1	0	0	0	1	2	13	[illegible]
...y 3																
...	1.27	1.10	2.43	2.53	0.11	0.38	4.46	5.02	[illegible]	3.10	3.72	4.00	2.51	2.98	0.84	1.35
...D	0.54	0.47	0.90	0.97	0.33	0.90	1.72	2.37	1.76	1.78	1.04	3.25	2.12	1.77	0.86	1.19
	0.5–2.5	0.5–2.0	1.0–4.5	1.0–4.0 (0.5)	0.5–1.5	0.5–4.0	1.5–10.0	2.0–12.0 (0.5)	0.5–8.5	0.5–9.0 (0.5)	0.5–8.5	0.5–17.0 (0)	0.5–1..0	0.5–7.0	0.5–3.0	(5.5) 0.5–4.0
...	37	30	38	30	37	29	37	20	28	30	33	30	37	[illegible]	37	27
... zeros	0	1	0	0	[illegible]	[illegible]	0	0	2	1	0	0	1	1	15	7
...ys 4–6																
...	1.34	1.05	2.71	2.43	0.34	0.21	4.36	3.88	3.55	3.28	3.93	3.83	3.35	3.07	1.12	1.40
...D	0.60	0.61	0.77	0.97 (0)	0.55	0.41 (3.5)	1.40	1.29 (10.0)	2.01	1.76 (11.0)	1.71	2.44 (0)	1.67	1.94	1.07	1.16
	0.5–2.5	0.5–2.5	1.0–4.0	1.0–5.0	0.5–2.0	0.5–2.0	2.0–9.0	1.5–7.5	0.5–9.0	1.0–8.0	1.0–8.0	0.5–13.0	1.0–8.0	0.5–6.0	0.5–4.5	0.5–4.0
...	38	30	38	30	38	[illegible]	38	[illegible]	38	30	38	30	37	30	37	30
... zeros	0	1	0	0	25	23	0	0	0	1	0	0	0	2	12	5
...p	0.01		< 0.001				< 0.001						< 0.05			

[s] q waves are included.

TABLE 8. *Rp/Sp ratio in 1/10 mV in intermediate and lowest atrial leads showing range and quartiles on the first and fifth or sixth day of life.*

Day	Group	i: I+II	i: III+IV	l: I+II	l: III+I
1	25 %	0.71	0.45	1.33	0.63
	50 %	1.00	0.75	2.00	1.83
	75 %	1.50	1.20	2.94	2.16
		0.38–	0.07	0.67	0.13–
		2.75	5.00	12.00	9.00
		38	30	34	21
	No. zeros	1	8	0	0
	No. ∞	0	0	13	1
5	25 %	0.50	0.63	0.92	1.00
	50 %	1.00	1.00	1.67	2.50
	75	1.61	1.27	2.83	3.50
		0.09–	0.17	0.33–	0.20–
		5.00	9.00	7.00	10.00
		34	30	37	30
	No. zeros	1	1	0	2
	No. ∞	0	0	12	5

Zeros and ∞ not included.

largest intrinsic, positive and negative waves in all recorded leads were also analysed. The largest intrinsic deflection was measured from the peak of the *Rp* wave to the peak of the *Sp* wave. The findings are similar. That is, lower mean[1] and maximum values are recorded in infants less than one hour of age. Increases from the first to the last examination tend to be limited to younger infants. The size of the deflections may be of considerable magnitude but the range is wide. Bengtsson maximum normal value of 0.6 mV was not infrequently exceeded. (Table 7.) There appears to be a direct relationship between the size of the largest intrinsic deflection and the amplitude of the *P* wa in lead II, that is, the larger the intrinsic deflection, the larger the *P* wave amplitude in lead II, but only on the first day of life ($p<.03$). The size of this deflection was, however not found to be related to any other tested parameter such as the infant weight, systolic blood pressure, heart volume nor as mentioned earlier duration of the *P* wave.

The *Rp/Sp ratio* was also determined in both intermediate and lowest atrial leads. In accord with the finding of significantly lower amplitude *Sp* waves in infants less than one hour of age these infants also tend to have a higher ratio in both leads on the first day. From the first to the last examination, a slight increase in median is only found in older infants ($p<.05$). As in adults [35], lower ratios are found in the higher lead, although newborns have lower amplitude *Rp* and higher amplitude *Sp* waves in atrial leads [28]. (Table 8.)

Additional later waves may also be present. Nine of one hundred infants had a late *r* with or without an *s*, at some time during the first week. In 7 this finding was confined to the lowest atrial and in 2 to the intermediate atrial lead. There was no other associated finding.

Direction of P Waves

In supra-atrial leads, all infants have a negative *P* wave both at birth and at the end of the week. Initially in the highest atrial lead, the majority of infants in Group I have diphasic w ves while the majority of infants in Group IV have negative *P* waves. The latter is also the case at the end of the week. In intermediate atrial leads, both initially and later all infants have diphasic *P* waves. This is also true of Group IV infants in lowest atrial leads on the first day of life although more than a quarter of the youngest infants have a positive wave in this lead.

[1] But just short of statistical significance.

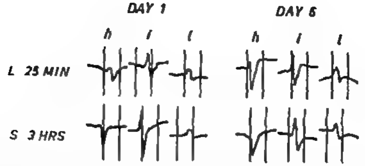


Fig 3. Esophageal P waves at highest (h) intermediate (i) and lowest (l) atrial levels. On the first day of life the amplitude of the P wave tends to be lower in younger than in older infants. At the end of the week, amplitudes are similar (tracing retouched).

infants less than one hour of age in supra-atrial (b) and atrial (h) leads ($p < .05$) but the same trend is present in intermediate and lowest atrial leads. Presumably for this reason individual and group increases in amplitude at the end of the week are either greater in, or limited to infants less than one hour of age on initial examination These changes with age are of statistical significance in supra-atrial (a) (b) and atrial (h) leads. As in the case of

But just short of statistical significance.

the Rp wave maximum values are recorded at the intermediate atrial level although large amplitudes also occur in highest atrial leads. The greatest Sp wave recorded at this level was 1.2 mV in a single infant on the third day of life In general amplitudes are smaller in lowest atrial leads. Below this level Sp waves are very uncommon. (Table 6 Fig 3)

As the greatest amplitude P waves are not necessarily seen in these leads the

TABLE 7 *Largest intrinsic positive and negative P deflections in 1/10 mV showing mean, standard deviation and range during the first week of life*

Day	Group	Largest intrinsic I + II	Largest intrinsic III + IV	Largest positive P I + II	Largest positive P III + IV	Largest negative P I + II	Largest negative P III + IV
	n	28	20	28	20	28	20
1	m	7.29	8.58	3.52	3.60	4 44	5.08
	s.d	3.06	2.94	1 55	2.71	1 96	2.38 (12.0)
		2.0–17 0	3.5–16 0	0 5–7 5	1 0–1 5	1 0–10.5	1 0–10.5
2	m	6 88	7 92	3.54	3.72	4.58	5.30
	s d	3.06	3.75 (2.5)	1 92	1 90 (1 0–10 0)	2.34	2.45
		2.0–16.0	4 0–22.0	0.5–9 0	1 5–9 0	0 5–13.0	[illegible] 5–14.5
3	m	7 78	8.63	4.28	4 00	5.48	6.02
	s d	[illegible].81	3.78	[illegible].5	1 69 (0.5–13 0)	2.83	2.92
	[illegible]	3.0–16 5	2.5–23.0	0 5–12.5	1 0–7 0	1 5–11 0	1 0–17 0
5–6	m	8.63	8.25	4 81	4.28	5.62	5.06
	s d	2 79	3.48	2.41	2.17	2.09	2 32
		4 0–17 5	3.5–20 0	1 0–11 0	1 5–11 0	3.0–11 [illegible]	2.0–13.0

Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

TABLE 10 *R amplitude (1/10 mv) in esophageal leads showing range and quartiles during first week of life*

Day	Group	E pre-atrial I II	E pre-atrial III IV	Infra-atrial b I II	Infra-atrial b III IV	Infra-atrial I II	Infra-atrial III IV	Infra-atrial d I II	Infra-atrial d III IV	Infra-atrial d I+II	Infra-atrial d III+IV
1	25	0.50	0.50	3.50	2.00	5.25	4.50	7.00	6.00	9.00	8.00
	50	1.00	1.00	6.00	4.00	7.25	7.25	9.00	9.50	10.75	10.50
	75	1.00	1.37	8.00	10.50	10.25	10.00	11.75	12.00	12.67	14.00
					(0.8–14.0)	(1.5)		(2.0)		(2.0)	
		0.5–1.5	0.5–1.5	0.5–17.0	1.5–13.0	2.0–22.0	1.5–14.5	4.0–21.0	3.5–17.0	4.5–21.0	4.5–17.0
		38	30	37	17	37	28	37	27	30	19
	No. zeros	21	14	0	0	0	0	0	0	0	0
2	25	0.50	0.50	4.25	4.87	5.00	6.00	8.62	7.00	8.00	8.50
	50	1.00	1.00	7.00	9.25	8.00	9.00	10.00	11.50	9.50	11.00
	75 %	1.50	1.00	8.00	12.62	10.00	12.00	11.00	15.00	12.50	12.00
				(0.5)	(1.0–14.5)	(1.0)	(2.0)				
		0.5–2.0	0.5–2.0	1.0–17.0	2.0–14.0	1.5–20.0	2.5–18.5	1.0–22.0	2.0–16.0	2.0–25.5	5.0–18.0
		38	30	29	19	37	28	36	27	23	19
	No. zeros	22	11	0	1	0	1	0	0	0	0
3	25	0.50	0.87	4.25	4.00	4.00	5.75	6.00	7.62	7.50	7.25
	50 %	1.00	1.00	7.00	8.00	7.75	8.50	9.00	10.00	9.50	10.00
	75 %	1.00	1.50	9.25	12.00	10.37	12.00	12.00	14.37	12.25	12.00
					(0.5)	(0.5)	(1.0)	(1.5)			
		0.5–2.0	0.5–2.5	0.5–17.0	2.0–15.0	1.0–20.5	2.0–17.5	2.0–21.5	1.0–22.0	3.5–20.5	1.5–16.0
		37	30	30	23	36	29	25	26	23	16
	No. zeros	21	12	1	0	0	0	0	0	0	0
5	25 %	0.50	1.00	4.12	5.25	4.25	5.75	5.37	7.50	6.12	8.37
	50 %	1.00	1.00	7.00	9.00	7.00	8.50	8.50	9.50	7.75	10.00
	75 %	1.50	1.50	8.87	11.00	10.00	11.12	11.00	12.25	9.50	12.12
					(1.0)		(0.5)	(2.0)	(0.5–15.0)		
		0.5–2.0	0.5–4.0	0.5–15.5	2.5–14.0	1.5–18.5	3.0–17.0	2.5–18.5	3.0–15.5	2.5–14.5	6.0–15.0
		[illegible]	30	34	25	37	30	30	25	16	14
	No. zeros	7	3	2	2	0	0	0	0	0	0
	p	<0.05	<0.01							<0.01	

Cases with *R* wave of 0.5 mm or more
R waves following an initial deep *Q* wave are listed as *R'*
Refers to significant difference from day 1 to 5–6.

Table 9 *Q amplitude in 1/10 mV in esophageal leads showing range and quartiles during first week of life.*

		Infra-Atrial							
		b		c		d		e	
Day	Group	I+II	III+IV	I+II	III+IV	I+II	III+IV	I+II	IIII+IV
1	25 %	1 62	1 50	1 00	1 00	0 50	1 00	0.50	0 87
	50 %	2.00	3.00	2.00	2.00	1 00	1 50	1 00	1 00
	75 %	3 00	3.50	2.50	2.87	.00	2.00	1 75	1.50
			(0 5)						
		0 5–4.5	1 0–4 5	0 5–4.0	0 5–4.5	0.5–3 0	0.5–3.0	0.5–.5	0 5–1.5
	n	27	17	37	28	37	27	30	19
	No zeros	3	2	8	4	13	8	13	9
2	25 %	1 00	1.50	1 00	1 00	1 00	1 00	0 50	1 00
	50 %	2.50	2.50	1 50	2.00	1 00	1 50	1 00	1.50
	75 %	3.50	3.50	2.00	3.50	2.00	2.50	1 87	1 75
									(2.0)
	r	0.5–4 5	1 0–4.0	0.5–3.0	0 5–5 0	0.5–.5	0.5–3.5	0.3–2.5	0.5–2.5
	n	29	19	37	28	36	27	23	19
	No zeros	2	1	9	5	17	12	11	10
3	25 %	1 00	2.00	1 00	1.50	0.50	0 87	0 67	1 00
	50 %	2.00	2.75	1.50	2.00	1 00	1 00	1 50	1 00
	75 %	3 00	3 50	3.00	2.50	1 87	1 62	1 87	1 12
					(5 0)				(0.5–2.5)
	r	0 5–3.5	0 5–4 0	0 5–4 0	0 5–3.5	0 5–4 0	0.5–4 0	0 5–2.5	1 0–1.3
	n	30	23	38	29	25	28	22	16
	No zeros	1	3	6	6	11	6	10	10
5–6	25 %	1 50	2.00	1 23	1 00	1 00	1 00	1 00	1 00
	50 %	2.50	2.50	2.00	2.00	1 50	2.00	1 00	1 25
	75 %	3.50	4.00	3 00	2.75	.00	2.50	1 75	1 8
	r	0 5–5.5	0 5–5.5	0 5–4.0	0 5–5.5	0.5–3.0	0 5–4 5	0 5–2 5	0 5–4.0
	n	34	26	37	30	30	26	16	14
	No zeros	1	1	4	1	6	3	3	6
	p					<0 05	<0 03	<0 05	

Cases with Q wave of 0.5 mm or more

Deep Q waves at higher levels are listed with S waves.

p Refers to significant differences from day 1 to 5–6

Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

Immediately below the atrium with few exceptions as noted above P waves are positive

The Ventricular QRS Complex[1]

Q Wave[2]

During the first few days Q waves are often not present in lowest infra-atrial leads. From the first to the last examination, the incidence of Q waves in these leads increases. There is little change in amplitude over this period although there

[1] The influence of the electrical axis and electrical position of the heart on the ventricular complex was not determined because only one infant in the first day of life had left axis deviation and horizontal position. Moreover no significant change in electrical axis occurred during the first week.

[2] In supra-atrial, atrial and high infra-atrial leads, Q and QS waves are listed with the S waves and R waves following an initial Q wave are listed as R′ Below this level initial negative deflections are listed as Q waves after a definite change in pattern has occurred and/or Q waves have significantly decreased in amplitude to 0 5 mV or less.

TABLE 10. R amplitude (1/10 mv) in esophageal leads showing range and quartiles during first week of life

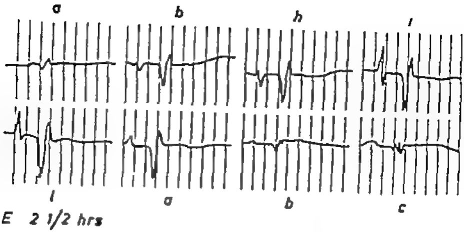
Day	Group	Supra-atrial I II	Supra-atrial III IV	Infra-atrial b I II	Infra-atrial b III IV	Infra-atrial I II	Infra-atrial III IV	Infra-atrial d I II	Infra-atrial d III IV	Infra-atrial I+II	Infra-atrial III IV
1	25%	0.50	0.50	2.00	2.00	5.25	4.50	7.00	6.00	9.00	8.00
	50	1.00	1.00	6.00	4.00	7.25	7.25	9.00	9.80	10.75	10.50
	75	1.60	1.37	8.00	10.50	10.25	10.00	11.75	13.00	12.67	14.00
					(0.5–14.0)	(1.5)		(2.0)		(2.0)	
		0.5–1.5	0.5–1.5	0.5–17.0	1.5–13.0	3.0–22.0	1.5–14.5	4.0–21.0	3.0–17.0	4.5–21.0	4.5–17.0
	n	23	30	27	17	27	28	37	27	30	19
	No. zeros	21	14	0	0	0	0	0	0	0	0
2	25	0.50	0.50	4.25	4.87	5.00	6.00	6.62	7.00	8.00	8.50
	50	1.00	1.00	7.00	9.25	8.00	9.00	10.00	11.50	9.50	11.00
	75	1.50	1.00	8.00	12.62	10.00	12.00	11.00	16.00	12.50	13.00
				(0.5)	(1.0–14.5)	(1.0)	(2.0)				
		0.5–2.0	0.5–2.0	1.0–17.0	2.0–14.0	1.5–20.0	2.5–18.5	1.0–28.0	3.0–16.0	2.0–25.5	5.0–18.0
	n	25	30	29	19	27	28	26	27	[illegible]	19
	No. zeros	23	11	0	1	0	1	0	0	0	0
3	25	0.50	0.87	4.23	4.00	4.00	4.75	6.00	7.62	7.50	7.25
	50%	1.00	1.00	7.00	8.00	7.75	8.50	9.00	10.00	9.50	10.00
	75%	1.00	1.50	9.25	12.00	10.27	12.00	12.00	14.37	12.25	12.00
					(0.5)	(0.5)	(1.0)	(1.5)			
		0.5–2.0	0.5–2.5	0.5–17.0	2.0–15.0	1.0–20.5	2.0–17.5	3.0–21.5	1.0–28.0	3.5–20.5	1.5–16.0
	n	27	30	30	23	26	29	26	28	[illegible]	[illegible]
	No. zeros	21	[illegible]	1	0	0	0	0	0	0	0
5	25%	0.50	1.00	4.12	5.25	4.25	5.75	5.37	7.50	6.12	8.37
	50%	1.00	1.00	7.00	9.00	7.00	8.50	8.50	9.50	7.75	10.00
	75%	1.50	1.50	9.87	11.00	10.00	11.12	11.00	12.25	9.50	12.12
					(1.0)		(0.5)	(2.0)	(0.5–16.0)		
		0.5–2.0	0.5–4.0	0.5–18.5	2.5–14.0	1.5–18.5	3.0–17.0	2.5–18.5	3.0–16.5	3.5–14.5	5.0–15.0
	n	28	30	[illegible]	[illegible]	27	30	30	26	16	14
	No. zeros	7	3	2	2	0	0	0	0	0	0
	p	<0.05	0.01							<0.01	

Cases with R waves of 0.5 mm or more

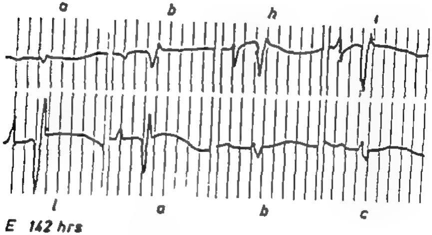
R waves following an initial deep Q wave are listed as R′

p Refers to significant differences from day 1 to 5–6

Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.



a.



b.

Fig. 4 Esophageal leads taken at supra-atrial (a b) atrial (h, i, l) and infra-atrial (a, b,) levels at ½ hours and at 14 hours. Note initial absence of an wave in upra-atrial lead (a), lower amplitude of the Q wave in trial leads (i, l) and appearance of $ST-T$ segment (These esophageal leads were aligned and then redrawn without modification.)

is a slight tendency to increase ($p < 05$) For the most part, larger deflections are seen in more proximal leads. (Table 9)

R Wave

Absence of an initial R wave 3 cm above the highest atrial lead is relatively common during the first few days of life—i e. 35 of 68 infants do not have this wave initially as compared to 10 of 68 infants at the end of the week The amplitude of this deflection tends to increase slightly with age Below this level an initial R wave is seldom seen.

In infra-atrial leads, R waves tend to be of greater amplitude in more distal leads and the highest values are more often recorded on the second or third day of life. From the first to the last examination, there is a tendency to small increases in proximal and decreases in distal leads ($p < 01$) (Table 10)

The amplitude of the Q and R waves exceeds that reported in adults [2] This has also been noted by Anibaldi *et al*

TABLE 11A *Q amplitude in 1/10 mV esophageal leads showing range and quartiles during the first week of life*

Day	Group	*Supra-atrial*				*Atrial*					
				b		h		c		y	
		I + II	III + IV	I + II	III + IV	I + II	III + IV	I + II	III + IV	I + II	III + IV
1	25	4.50	4.37	9.00	8.50	11.87	11.00	13.12	13.12	13.75	13.00
	50	5.75	6.00	11.25	10.00	14.50	13.50	16.00	15.75	16.50	16.00
	75	6.12	7.50	14.12	12.62	16.12	16.00	20.00	19.00	21.50	17.75
									(9.0)	(4.5)	(6.0–24.0)
		0.8–14.0	3.0–12.0	5.5–19.0	5.0–16.5	7.0–22.0	7.5–24.0	10.0–31.5	9.5–34.0	6.5–27.5	8.5–22.5
	n	28	30	28	30	28	28	28	30	27	[illegible]
	No. zeros	0	0	0	0	0	0	0	0	0	0
2	25	4.50	5.00	9.00	8.00	9.37	12.37	14.00	14.00	14.00	13.00
	50	5.50	6.25	11.00	11.75	14.25	15.50	16.25	19.00	16.00	17.00
	75%	7.50	8.12	12.50	14.25	16.75	17.75	19.00	21.50	19.25	21.00
		(0.5)	(3.0)	(0)					(9.5)	(7.5)	(7.0)
		1.5–15.5	2.5–14.0	4.0–19.0	8.0–24.0	7.0–22.0	9.0–27.0	10.5–24.0	11.0–26.5	9.0–27.5	10.5–28.0
	n	33	30	29	30	38	30	28	27	37	25
	No. zeros	0	0	0	0	0	0	0	0	0	0
3	25%	4.25	5.00	9.37	9.37	12.75	12.75	16.87	16.87	14.75	13.25
	50%	5.50	6.00	12.00	12.00	15.25	16.50	19.25	18.75	17.00	17.75
	75%	8.00	7.50	14.12	18.00	18.12	20.25	22.12	22.25	20.25	21.00
		(0.5)							(29.0)		
		2.0–12.0	2.5–13.0	4.0–20.5	5.0–30.5	7.0–25.0	9.0–26.0	11.0–28.0	10.0–26.5	6.5–27.5	8.5–25.0
	n	37	30	28	30	26	29	28	30	33	23
	No. zeros	0	0	0	0	0	0	0	0	0	0
5–6	25%	4.50	5.87	10.00	11.00	14.37	14.00	16.37	16.50	12.00	13.87
	50%	6.00	8.00	12.00	13.25	16.25	17.00	19.25	20.00	18.00	16.50
	75%	8.00	9.62	16.25	16.50	19.62	20.00	21.12	24.25	21.12	20.00
			(1.5)							(8.0)	(8.0)
		1.0–15.0	3.0–12.0	7.0–20.5	5.5–22.5	8.5–27.0	7.0–27.0	10.0–34.0	10.5–31.0	7.0–37.0	9.5–46.5
	n	33	30	26	30	38	29	33	30	33	30
	No. zeros	0	0	0	0	0	0	0	0	0	0
	P			<0.05	<0.001	<0.01	<0.001	<0.001	<0.001		

TABLE 11B

Day	Group	I fra-atrial a I + II	a III + IV	b I + II	b III + IV	c I + II	c III + IV	d I + II	d III + IV	e I + II	e III + IV
1	25 %	8 75	0 50	1 87	-.75	1 50	1 00	.50	1 00	3 00	4 87
	50 %	13.00	11 7	3 00	5 50	3.50	3 00	4 00	4 00	4.50	5.50
	75 %	10 00	17 00	7.50	10 00	5.50	0 —	5.50	0.00	7 00	7 1
		(4 0)	(1 5)				(0.5)				
		4.5 23 0	3.0-21 0	0.5-13 0	0.5-15 0	0.5-13 0	0.5-8.5	1 0-12.0	0 5-13 5	0 5-12.0	0 5-11 0
	n	[illegible]	20	38	28	37	29	37	7	30	19
	No zeros	1	1	6	7	4	8	2	4		1
2	25 %	9 12	10 37	-.00	3.00	1 50	2.50	.37	.00	3 00	.75
	50	13.50	15 00	4 50	5.50	-2.	3.50	4 00	4 50	5 25	5 00
	75 %	16 25	21 00	7 00	9 00	5 00	5.50	6 50	6 75	7 00	7 00
		(5 0)	(3.5)								(1 0)
		6.0-19 5	5 0-24 0	0 5-11 0	0.5-17 0	0.5-13.5	0 5-15.0	0 5-10 5	0.5-12.0	1 0-17 5	.5-11 0
	n	38	30	38	30	37	20	36	7	23	19
	No. zeros	2	0	13	8	0	8	2		1	0
3	25 %	9 25	8 00	2.00	2.00	1 50	1 00	2.00	-.00	3.00	2.00
	50 %	12 25	12.25	4 00	3.25	2.50	4 25	3.75	4 00	4 50	.50
	75	15 37	15.50	6 00	5.00	3.50	5.50	5 00	5. 5	7 00	5.62
			(1 0)						(1 0)		
		1 5-20 0	2.5-30 0	0.5-13.0	0 5-15 0	0 5-10 0	0 5-11 0	1 0-13.0	1 5-11 0	0 5-13.0	0 5-7 5
	n	38	30	38	29	36	20	35	*9	23	10
	No. zeros		2	11	6	7	5	5	3	2	2
5-6	25 %	6 00	8.00	1.37	-.25	1 87	1.50	2.00	.00	.00	2 00
	50 %	10 25	11 75	2 5	2.50	2 00	2 50	2 75	3 50	3.00	4 00
	5 %	13.75	14 87	4 75	5.00	4 00	4.50	5.00	5 50	5 00	5 00
			(1 0)								
		0 5-21 0	[illegible] 0-31 0	0 5-8 0	0.5-9 0	0.5-9 0	0.5-6 0	0 5-11 0	0 5-8.0	0 5-9 0	1 5-9 0
	n	37	29	38	30	37	29	30	28	10	14
	No. zeros	1	1	8	9	3	5	2	5	1	3
	p	<0 001									

Cases with S wave 1 0.5 mm more

Q and QS waves in these leads are included

p Refers to significant differences from day 1 to 5-6

Figures in parentheses indicate minimum and maximum values in infants *without* all 4 examinations

TABLE 1.—*R′ amplitude in 1/10 mV in esophageal leads showing range and quartiles during the first week of life.*

		Supra-atrial		*b*		*Atrial* *h*				*r′*		*Infra-atrial*	
Day	Group	I II	III IV	I II	III IV	I II	III IV	I II	III IV	I II	III + IV	I + II	III + IV
1	25 %	2.00	2.00	3.00	3.50	4.00	4.50	5.00	5.50	8.25	6.50	6.37	8.50
	50 %	3.00	3.00	4.25	5.50	5.00	7.00	7.00	9.00	11.50	11.00	10.50	10.50
	75 %	4.50	4.12	6.50	6.00	7.37	8.50	9.50	13.25	16.25	17.50	16.00	[illegible]
					(11.0)		(1.0–12.5)		(25.0)	(0.5)	(36.0)	(0.5)	
		0.5–9.0	0.5–7.0	0.5–8.5	0.5–9.0	0.5–10.5	1.5–12.0	0.5–17.0	1.0–24.0	1.5–22.0	1.0–23.0	2.0–24.0	1.5–22.5
	n	38	30	38	30	34	29	38	30	34	31	27	27
	No. zeros	2	4	2	1	2	1	1	0	1	0	2	0
2	25 %	1.62	2.25	4.00	2.87	5.00	4.37	6.37	6.00	9.75	10.00	9.00	10.00
	50	2.75	3.50	5.00	5.25	6.00	7.75	8.00	8.50	14.25	14.00	12.50	12.50
	75 %	5.37	4.50	7.00	7.00	8.50	9.00	11.50	11.00	17.87	21.25	18.00	17.25
			(1.0)		(0–10.5)		(13.0)	(1.5)	(24.0)	(1.0–30.0)	(1.0–24.0)	(1.0)	(1.0)
		0.5–8.5	1.5–7.5	1.5–11.0	0.5–9.5	1.0–12.0	1.5–11.5	2.0–16.5	2.5–15.0	2.0–28.5	5.0–32.0	3.0–28.5	2.0–37.0
	n	38	30	38	30	33	30	30	[illegible]	34	26	30	30
	No. zeros	6	5	1	0	0	0	0	0	0	0	1	1
3	25 %	2.50	2.00	4.12	3.87	3.00	4.50	5.87	7.00	10.25	10.87	10.25	9.50
	50 %	2.75	3.00	5.50	5.25	4.00	7.00	8.25	9.00	16.00	17.00	14.00	14.00
	75 %	5.50	5.00	7.00	7.62	6.62	9.00	11.25	12.00	19.50	24.75	19.50	23.00
			(0.5)				(14.0)		(2.0–22.5)				
		0.5–8.5	1.0–7.0	0.5–14.0	0.5–10.5	2.0–10.0	1.5–11.0	1.5–24.0	2.5–17.0	1.0–21.5	3.5–44.0	2.5–25.0	1.0–30.0
	n	[illegible]	30	29	30	37	29	28	30	[illegible]	28	35	26
	No. zeros	5	3	2	0	2	0	0	0	0	0	2	1
5–6	25 %	1.50	2.00	3.50	2.87	2.00	2.00	4.50	4.12	8.00	7.87	8.75	6.87
	50 %	2.50	2.50	4.50	4.00	5.25	4.00	6.00	6.25	12.00	10.50	10.75	11.50
	75 %	4.37	3.87	5.50	5.50	7.00	5.75	10.25	7.87	19.00	15.12	14.62	16.75
					(0)		(1.0–9.5)		(20.0)				(0)
		0.5–6.5	0.5–9.0	1.0–9.0	0.5–8.5	0.5–8.5	1.5–9.5	0.5–17.5	1.0–14.0	2.5–36.0	2.5–30.0	2.5–24.0	1.0–31.0
	n	38	30	38	30	38	29	[illegible]	[illegible]	27	30	31	26
	No. zeros	2	2	2	0	2	0	1	2	2	0	2	0
	p						< 0.01		< 0.01				

Cases with R′ of 0.5 mm or more.
R waves following an initial Q wave are listed as R′.
p Refers to significant differences from day 1 to 5–6.
Figures in parentheses indicate minimum and maximum values in infants without all 4 examinations.

TABLE 11B

Day	Group	*Infra-atrial* *a* I + II	*a* III + IV	*b* I + II	*b* III + IV	*c* I + II	*c* III + IV	*d* I + II	*d* III + IV	*e* I + II	*e* III + IV
	25 %	8.75	0.50	1.87	2.73	1.50	1.00	2.50	1.00	3.00	4.87
	50 %	13.00	11.7	2.00	5.50	3.50	3.00	4.00	4.00	4.50	5.50
	75 %	16.00	17.00	7.50	10.00	5.50	6.25	5.50	6.00	7.00	7.12
		(24.0) 4.5–23.0	(1.5) 2.0–21.0	0.5–13.0	0.5–15.0	0.5–13.0	(9.5) 0.5–8.5	1.0–12.0	0.5–13.5	0.5–12.0	0.5–11.0
	n	38	29	38	28	[illegible]	29	3	27	[illegible]	10
	N zeros	1	1	6	7	4	8	2	4	2	1
2	25 %	9.12	10.37	2.00	2.00	1.50	2.50	2.37	2.00	3.00	2.75
	50 %	13.50	15.00	4.50	5.50	2.25	3.50	4.00	4.50	5.25	5.00
	75 %	16.25	21.00	7.00	9.00	5.00	5.50	6.50	6.75	7.00	7.00
		(5.0) 6.0–19.5	(2.5) 5.0–24.0	0.5–11.0	0.5–17.0	0.5–13.5	0.5–15.0	0.5–10.5	0.5–13.0	1.0–17.5	(1.0) 2.5–11.0
	n	38	30	38	30	37	29	36	27	23	19
	N zeros	2	0	13	8	9	8	2	2	1	6
3	25 %	9.25	8.00	2.00	2.00	1.50	1.00	2.00	2.00	3.00	2.00
	50 %	12.25	12.25	4.00	3.25	2.50	4.25	3.75	4.00	4.50	2.50
	75 %	15.3	15.50	0.00	5.00	3.50	5.50	5.00	5.25	00	5.62
		1.5–26.0	(1.0) 2.5–30.0	0.5–13.0	0.5–15.0	0.5–16.0	0.5–11.0	1.0–13.0	(1.0) 1.5–11.0	0.5–13.0	0.5–7.5
	n	38	30	38	20	20	20	25	29	22	10
	N zeros	2	2	11	6	7	5	5	3	2	2
5–6	25 %	6.00	6.00	1.27	2.25	1.87	1.50	2.00	2.00	2.00	2.00
	50 %	10.25	11.75	2.25	3.50	2.00	3.50	3.75	2.50	3.00	4.00
	75 %	13.75	14.87	4.75	5.00	4.00	4.50	5.00	5.50	5.00	5.00
		0.5–21.0	(1.0) 2.0–31.0	0.5–8.0	0.5–9.0	0.5–9.0	0.5–6.0	0.5–11.0	0.5–8.0	0.5–6.0	1.5–6.0
	n	37	29	38	30	37	[illegible]	30	26	10	14
	N zeros	1	1	8	9	3	5	2	5	1	[illegible]
	p	< 0.001									

Cases with S wave of 0.5 mm or more.
Q and QS waves in these leads are included.
p Refers to significant differences from day 1 to 5–6.
Figures in parentheses indicate minimum and maximum values in infants *without* all 4 examinations.

finding was present at birth and at the end of the week in one infant and only at the end of the week in the other.

A QR pattern, characteristic of atrial leads, was seen in 6 infants 2 cm above the highest atrial and in 3 infants 1 cm below the lowest atrial lead, but not present at these levels in any infant at the end of the week. In other words, the area over which this complex is inscribed decreases. Four infants did not have a QR in any lead at birth as compared to 11 infants at the end of the week.

A qr in supra-atrial leads was seen in 3 infants in Groups I and II initially. It persisted in one until the end of the week and was first noted in another at the end of the week, although it may have been present earlier, an insufficient number of higher leads being available.

Unlike adults who have either a QS or QR in atrial leads (28), only 7 infants had a QS on the first day of life. Those one hour old or less tended to have this pattern in the highest atrial or 1 cm above this lead. This finding persisted in 2 infants at the end of the week. These infants were among the few (1 %) who did not have a secondary r wave in supra-atrial leads at the end of the week, even though some had had it earlier.

The incidence of deep S waves (not including QS waves) at any level increases with age, i.e., they are present in 31 infants on the first day as compared to 50 of 68 infants at the end of the week.

Although patterns vary significantly at different levels and to some extent on different days during the week, they are sufficiently characteristic to permit recognition of the approximate location of the lead.

Resemblance Between Esophageal and Routine Electrocardiographic Leads

Determination of resemblance of esophageal leads to the other 16 leads (standard bipolar, unipolar and precordial) has been fairly strictly interpreted, requiring P and T waves in the same direction as well as relatively similar amplitudes and ratios of the R and S waves. Therefore, the number of esophageal leads not resembling any other lead is probably greater in this study. As there did not appear to be any significant differences, the groups were combined for analysis.

The majority of leads adjacent to the atrium tend not to resemble any lead, while those above the atrium resemble lead aVR more than any other, but are seldom identical. In only a few instances does the QRS complex of supra-atrial leads resemble leads I, aVL or V_6. Little change takes place during the week. Scattergrams relating the R/S ratios* in lead aVR and supra-atrial lead (s) also suggest a direct linear relationship, especially at the end of the week. During this period little change in the ratio is found in the esophageal lead, but the ratio decreases significantly in lead aVR (i.e. a ratio of 2:1 or more is present in 24 infants initially as compared to 8 of 68 infants at the end of the week).

In the lead immediately below the atrium on the first day, only 6 of 67 infants have a pattern resembling some other lead, i.e., III, aVF and II in this order. At the end of the week, 13 of 68 infants have a pattern resembling either lead aVF or III.

* The late R was used in determining the ratio in both leads.

S Wave[1]

In supra-atrial and atrial leads values are generally higher in Group I and II infants initially (but not of statistical significance) and the amplitude increases gradually during the first week of life ($p < 01 - < 001$)

In infra-atrial leads amplitudes tend to be lower in younger infants (Groups I and II) initially but again not of statistical significance and gradually decrease during the week in infra-atrial lead (*a*) ($p < 001$) Absence of this wave is not uncommon 3 to 5 cm below the lowest atrial lead. (Table 11)

R'

On the first day in atrial leads and the lead immediately below the atrium amplitudes are lower (though not significantly) in infants in Groups I and II The size of these deflections increases in the middle of the week and then decreases again but is significant only in atrial leads (*h* *i*) in older infants. Progressive increase in size of this wave occurs with passage of the electrode more distally to lowest atrial and infra-atrial leads. (Table 12) In supra-atrial and mid atrial leads the R'/S or R/Q ratio is generally less than 1 0 In infra atrial lead (*a*) a ratio of 2 0 or more was seen in 10 infants at the end of the week In infra-atrial lead (*d*) and/or (*e*) 3 infants had a Q of 0 4 mV or more in 2 the voltage of the Q exceeded 25% of that of the R which in adults is often ascribed to myocardial infarction [28] (Fig 4)

QRS Patterns

For purposes of determining changes in patterns deflections measuring 4 5 mm (0 45 mV) or less are arbitrarily classified as a small *q* *r* or *s* wave As the electrode is advanced the following complexes are more commonly registered in the order mentioned

1 Supra-atrial level:
- *qr* or *rsr* — 3 to 5 cms from the nares.
- *rSr*
- *rSR* — proximal to the atrium.

2 Atrial level:
- *Qr*
- *QR*

3 Infra-atrial level[2]:
- *QR* — 1 cm below the atrium
- (*q*)*Rs* or (*q*)*R* — 3 to 5 cms below the atrium
- (*q*)*RS* — lowest leads.

Distinctive complexes are therefore registered at these 3 main levels, although some overlap of patterns in adjoining regions is common. Apart from atrial leads however there is considerable variation in appearance of complexes. This is most marked 3 to 5 cm below the atrium, the same area in which the greatest decrease in amplitude of deflections also occurs.

With few exceptions, if the initial deflection is a small *r* wave in higher supra-atrial leads an initial small *q* wave is seen in gastric leads, and vice versa.

The only 2 infants with a *qR* in supra-atrial leads are also the only infants with an *rS* in infra-atrial leads. In both instances the latter complex resembles that found in leads II and aVF and in one infant it is also present in lead aVL. This

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[1] See p 18 note 2.

[2] Parentheses indicate that the *q* wave may or may not be present

finding was present at birth and at the end of the week in one infant and only at the end of the week in the other

A QR pattern, characteristic of atrial leads, was seen in 6 infants 3 cm above the highest atrial and in 3 infants 1 cm below the lowest atrial lead, but not present at these levels in any infant at the end of the week. In other words the area over which this complex is inscribed decreases. Four infants did not have a QR in any lead at birth as compared to 11 infants at the end of the week.

A ɥr in supra-atrial leads was seen in 3 infants in Groups I and II initially It persisted in one until the end of the week and was first noted in another at the end of the week, although it may have been present earlier an insufficient number of higher leads being available.

Unlike adults who have either a QS or QR in atrial leads (28), only 7 infants had a QS on the first day of life Those one hour old or less tended to have this pattern in the highest atrial or 1 cm above this lead. This finding persisted in 2 infants at the end of the week. These infants were among the few (12%) who did not have a secondary r wave in supra-atrial leads at the end of the week, even though some had had it earlier

The incidence of deep S waves (not including QS w ves) at any level increases with age i they are present in 31 infants on the first day as compared to 50 of 68 infants t the end of the week.

Although patterns vary significantly at different levels and to some extent on different days during the week, they are sufficiently characteristic to permit recognition of the approximate location of the lead.

Resemblance Between Esophageal and Routine Electrocardiographic Leads

Determination of resemblance of esophageal leads to the other 10 leads (standard bi-polar unipolar and precordial) has been fairly strictly interpreted, requiring P and T waves in the same direction as well as relatively similar amplitudes and ratios of the R and S waves. Therefore, the number of esophageal leads not resembling any other lead is probably greater in this study As there did not appear to be any significant differences, the groups were combined for analysis.

The majority of leads adjacent to the atrium tend not to resemble any lead, while those above the atrium resemble lead aVR more than any other but are seldom identical. In only a few instances does the QRS complex of supra-atrial leads resemble leads I aVL or V_6 little change takes place during the week Scattergrams relating the R/S ratios[1] in lead aVR and supra-atrial lead (a) also suggest a direct linear relationship, especially at the end of the week. During this period little change in the ratio is found in the esophageal lead, but the ratio decreases significantly in lead aVR (i.e a ratio of 2.1 or more is present in .4 infants initially as compared to 8 of 68 infants at the end of the week).

In the lead immediately below the atrium on the first day only 6 of 67 infants have a pattern resembling some other lead, i.e., III, aVF and II in this order At the end of the week, 13 of 66 infants have a pattern resembling either lead aVF or III.

[1] The late R was used determining the ratio in both leads.

In infra-atrial lead (*b*) half of the infants have complexes resembling either lead II or aVF (equal numbers) less than half no lead and 4 either lead III or V_6. At the end of the week, more than 3/4 s of the cases have complexes resembling lead II or aVF less than 1/4 no lead and the remainder leads III and V_6.

In infra-atrial lead (*c*) 2/3 s of the infants have complexes resembling lead II or aVF (but 2/3 s of these are like lead II) less than 1/5th no lead and the rest resemble leads V_6, V_1 and V_4R (in this order). At the end of the week only 8 cases do not resemble either leads II or aVF.

In infra-atrial lead (*d*) on the first day 2/3 s of the cases resemble lead II or aVF (2/3 s lead II). Of the remainder 5 resemble right and 5 left chest leads. At the end of the week 3/4 s of the infants have complexes resembling lead II or aVF (2/3 s lead II) 4 have complexes resembling right and 4 left precordial leads.

In infra-atrial lead (*e*) on the first day ½ of the infants have complexes resembling lead II 1/6th no lead 8 have complexes resembling a right and 6 a left precordial lead, and only a very few leads aVF or III. The distribution is similar at the end of the week.

Scattergrams show a direct linear relationship between amplitudes of *Q*, *R* and *S* waves in infra-atrial leads (*c*) and (*d*) with amplitudes of *Q*, *R* and *S* waves in leads II and aVF on the first and last day of the week.

S–T Junction and Segment

Because of the difficulty in obtaining level baselines, quantitative evaluation of deviation of the *S–T* junction and *T* wave amplitude is not possible. On the *first day* in supra-atrial leads, the *S–T junction* is not displaced in the majority is depressed in most of the others, and elevated in 7 infants (range ±0.05 mV with the exception of 2 cases of 0.1 mV each). In atrial leads there is no deviation in the majority and more often depression in higher and elevation in lower leads with a range of ±0.15 mV in all except one infant (0.2 mV). With more distal passage of the electrode in infra-atrial leads, the range of deviation of the *S–T* junction decreases from ±0.15 mV (maximum 0.2 mV in one infant) to ±0.1 mV (maximum 0.15 mV in one infant).

At the *end of the week* in supra-atrial leads only 2 infants have positive displacement of the *S–T* junction and in all others there is either no deviation or depression of 0.1 mV. In atrial leads, the take-off of the *S–T* junction is displaced in less than 1/3 of the infants, depressed in higher and elevated in lower leads by ±0.25 mV. There are however 3 cases of elevation to 0.3 to 0.35 mV one to as much as 0.8 mV and one of depression to 0.45 mV. In infra-atrial leads, there is no deviation of the *S–T* junction in the majority of infants while most of the others have positive displacement except for 2 infants with negative displacement in distal leads. As had been observed on initial examination, the range decreased from ±0.15 mV (maximum +0.25 mV in one infant) in proximal leads, to ±0.05 mV in more distal leads.

The *S–T segment*[1] often seems somewhat elevated particularly in atrial leads. There

[1] With rapid heart rates the *Tp* wave can cause an apparent depression of the *S–T* segment.

is often a small negative or positive wave following the QRS complex which appears to be a Ta wave, possibly more frequent in atrial and lower infra-atrial leads. Landtman [30] described in premature infants small extra waves following the QRS complex which he attributed to artefacts from muscular activity. It seems unlikely that these waves are artefacts here. In some instances, the segment has a bizarre fall-away contour which arises from a curious relationship to the P wave.

T Wave

On the *first day of life*, T waves are more often positive in distal and negative in proximal leads. As a result, in the lowest infra-atrial leads, only 0 infants have inverted T waves while positive waves are found in 25 infants in infra-atrial lead ( ); 11, 14 and 5 infants in atrial leads (*l*), ( ) and (*h*); 4 and 1 infants in supra-atrial leads (*b*) and (*a*) (the latter measuring 0.03 mV). Infants in Group IV tend t have a greater number of positive T wa es in higher leads than do those in Group I.

At the *end of the week*, the number of positiv deflections increases especially in trial nd high infra-atrial leads and decreases in the lowest infra-atrial lead. However the tendency for T wav di rection *not* to change during this period is statistically significant in most leads (supra-atrial ( ), (*b*), atrial(*h*) ($p < .001$), infra-atrial ( ) (p 03), (*b*), (*c*), (*d*) and ( ) (p 001)).

At *birth*, the amplitude of the T wave ranges from +0.5 mV to −0.3 mV in supra-atrial leads, ±0.45 mV in atrial leads, ±0.5 mV in higher infra-atrial leads and +0.35 mV to −0.1 mV in infra-atrial leads (*d*) and (*e*). At the *end of the week*, amplitude ranges from +0.25 mV to −0.7 mV in supra-atrial leads, +0.8 to −0.35 mV in atrial leads, +0.85 to −0.15 mV in higher infra-atrial leads, and +0.35 to −0.2 mV in lower infra-atrial leads.

The contour of the T wave is often bizarre especially at atrial levels: sometimes wide and coved, or notched, or else with a slurred, ascending or descending limb. (Fig. 4.)

There appears to be direct relationship bet een the amplitude of the T ve in atrial esophageal leads and leads V and V_2, but only on the first day of life.

U Wave

At times, baseline wandering especially in peri-atrial leads, makes it difficult to determine the presence or absence of U waves. But as the incidence in adjacent leads is consistent, the data is presented. All questionable cases were excluded, and, probably for this reason, the majority of infants had no U waves at most levels on the first and last examination. With almost no exception, inverted waves are present in supra-atrial leads and not in infra-atrial leads, and no change occurs during the week. On the other hand, positive waves are seldom seen in supra-atrial leads and are most common in atrial (*s*), (*l*), infra-atrial (*a*) and (*b*) leads with an increase in incidence at the end of the week.

Discussion

From this investigation it is apparent that a fairly regular sequence of esophageal patterns is recorded at different levels but deviations are not uncommon. In-

In infra-atrial lead (*b*) half of the infants have complexes resembling either lead II or aVF (equal numbers) less than half no lead, and 4 either lead III or V_6. At the end of the week, more than 3/4 s of the cases have complexes resembling lead II or aVF less than 1/4 no lead and the remainder leads III and V_6.

In infra-atrial lead (*c*) 2/3 s of the infants have complexes resembling lead II or aVF (but 2/3 s of these are like lead II) less than 1/5th no lead and the rest resemble leads V_6, V_1 and V_4R (in this order). At the end of the week only 6 cases do not resemble either leads II or aVF.

In infra-atrial lead (*d*) on the first day 2/3 s of the cases resemble lead II or aVF (2/3 s lead II). Of the remainder 5 resemble right and 5 left chest leads. At the end of the week 3/4 s of the infants have complexes resembling lead II or aVF (2/3 s lead II). 4 have complexes resembling right and 4 left precordial leads.

In infra-atrial lead (*e*) on the first day ½ of the infants have complexes resembling lead II. 1/6th no lead. 8 have complexes resembling a right and 6 a left precordial lead, and only a very few leads aVF or III. The distribution is similar at the end of the week.

Scattergrams show a direct linear relationship between amplitudes of *Q*, *R* and *S* waves in infra-atrial leads (*c*) and (*d*) with amplitudes of *Q*, *R* and *S* waves in leads II and aVF on the first and last day of the week.

S–T Junction and Segment

Because of the difficulty in obtaining level baselines, quantitative evaluation of deviation of the *S–T* junction and *T* wave amplitude is not possible. On the *first day* in supra-atrial leads, the *S–T junction* is not displaced in the majority. It is depressed in most of the others and elevated in 7 infants (range ± 0.05 mV with the exception of 2 cases of 0.1 mV each). In atrial leads, there is no deviation in the majority and more often depression in higher and elevation in lower leads with a range of ± 0.15 mV in all except one infant (0.2 mV). With more distal passage of the electrode in infra-atrial leads, the range of deviation of the *S–T* junction decreases from ± 0.15 mV (maximum 0.2 mV in one infant) to ± 0.1 mV (maximum 0.15 mV in one infant).

At the *end of the week*, in supra-atrial leads, only 2 infants have positive displacement of the *S–T* junction and in all others there is either no deviation or depression of 0.1 mV. In atrial leads, the take-off of the *S–T* junction is displaced in less than 1/3 of the infants, depressed in higher and elevated in lower leads by ± 0.25 mV. There are however 3 cases of elevation to 0.3 to 0.35 mV, one to as much as 0.8 mV and one of depression to 0.45 mV. In infra-atrial leads there is no deviation of the *S–T* junction in the majority of infants while most of the others have positive displacement except for 2 infants with negative displacement in distal leads. As had been observed on initial examination, the range decreased from ± 0.15 mV (maximum $+0.25$ mV in one infant) in proximal leads, to ± 0.05 mV in more distal leads.

The S–T segment[1] *often seems* somewhat elevated particularly in atrial leads. There

[1] With rapid heart rates the *Tp* wave can cause an apparent depression of the *S–T* segment.

It is therefore of interest that left atrial pressure is not only elevated at birth, but the curve resembles that seen in adults with mitral incompetence. Sodi-Pallares & Calder [43] believe that QS complexes in leads I and aVL may also be due to left atrial dilatation. However P wave duration was not necessarily prolonged in the 9 infants with this pattern in lead I[1] 5 of whom had it on the first day. It was not seen after the age of 53 hours.

The conventionally recorded surface P wave cannot be considered to be an optimal representation of atrial electrocardiographic activity. Moreover the value of esophageal leads in arrhythmias is dependent on considerable amplification of the atrial complex with relatively minor amplification of the ventricular complex. As P waves are small and therefore difficult to measure exactly in conventional leads [11], especially at normal standardization, this selective increase in P wave amplitude in esophageal leads could be put to good advantage if it could be shown to depend on size of or pressure within the left atrium. This might be of special interest in the differential diagnosis of congenital heart disease or the respiratory distress syndrome because roentgenographic evaluation of size of this chamber is difficult at this age [2].

In an attempt to evaluate this, simultaneous recordings of esophageal electrocardiograms and atrial pressure recordings[2] were taken in 6 healthy infants on the first day of life. No relationship was found between P wave amplitude (Rp, Sp, largest intrinsic deflection, largest negative and positive P waves) in esophageal leads and mean atrial pressure in either the left or the right atrial chamber, but the group is too small for any definite conclusion. The results of other studies relating P wave amplitude to atrial size and pressure are also conflicting. Gordon *et al.* [24], using heart specimens, found a negative correlation between P wave amplitude and left atrial volume—that is, the lower the P wave amplitude the greater the left atrial volume; while both Escobar *et al.* [21] and Testelli [46] were unable to find a relation between height of P waves in the left atrium and the left atrial pressure. Dodge & Sandler [20] also found a poor relation between left atrial volume, measured on biplane angiocardiograms, and left atrial pressure. However these findings in adults may not be applicable to newborn infants.

However, a number of investigations have described changes in the esophageal electrocardiogram in patients with left atrial enlargement of different etiology. According to Conte & Fusaro [14], the following criteria constitute *definite* evidence of left atrial enlargement: 1) increased area of recording of atrial leads (also noted by Benoit & Rodriguez Alvarez [6]), 2) increased amplitude of the Rp wave [23, 37] and 3) increased ratio of the P–R_{II}/iQ intervals [53]. Less certain evidence of left atrial enlargement is furnished by the following: 1) increased amplitude of the Sp wave [13] and 2) increased duration of DI (= Q–Rp interval

[1] One infant also had QS in aVL.

[2] Cardiac catheterization performed by Dr H. Arcilla.

[3] The size of the left atrium also does not appear to be related to the mean electrical axis of the P [47].

[4] P–R_{II}/iQ interval: ratio of P–R interval in lead II to interval from onset of atrial intrinsic deflection (i) to ventricular esophageal Q wave.

sertion of the electrode to a specific distance from the nares *is not satisfactory* because as discussed earlier levels vary directly with length. *Instead the* location of the transitional complex of the P wave should first be *determined* According to Frau [23] this corresponds to the distance (cm) measured from the superior portion of the cricoid cartilage to the base of the xyphoid process multiplied by the coefficient 1 33 (Lewis rule) As significant alterations in complexes occur with minimal displacement of the electrode *recordings* should be taken at 1/2 cm intervals *over* a distance of at least 5 cm above and below this point. Multiple simultaneous bipolar leads are probably preferable

In newborns with late clamping of the umbilical cord atrial pressures are elevated during the first hour of life and left atrial pressure curves show prominent *v* waves [8 10] According to the former authors [8] this may be the result of low distensibility characteristics of the left heart chambers particularly of *the left atrium and to failure of* this chamber to effectively dilate immediately following the increase in pulmonary blood flow after birth This region may be comparatively blind on conventional electrocardiography but the esophagus is a convenient and safe route for obtaining semi-direct leads of the left atrium without resorting to more complex procedures such as intracardiac catheterization Study of the posterior aspect of the heart is important in the newborn because during the transition from fetal to neonatal existence increase in the pulmonary circulation and presence of a left-to-right shunt through the ductus arteriosus must necessarily place an increased load on the left heart.

There is suggestive evidence that the routine electrocardiogram reflects some of the changes associated with hemodynamic adaptation to extrauterine life and *it does* not seem unreasonable to *suppose that* some of these changes should also be noted on the esophageal electrocardiogram For example, a particular *pattern of* change is seen in infants with late *clamping of the* umbilical cord, especially on the first day of life. At birth most electrocardiographic intervals (P wave duration P–R interval QRS interval Q–Tc interval) are prolonged and amplitude of R waves over the right and S waves over the left chest is increased. After the first hour of life the mean T vector shifts to the right and anteriorly [25 51] The genesis of some of these findings has been ascribed to initial systolic overload of the right ventricle followed by transient physiologic overload of the left ventricle. These changes accompany decrease in pulmonary vascular resistance after lung inflation, increase in systemic resistance with cessation of placental circulation and reversal of flow through the ductus arteriosus.

Statistically significant changes in duration of intervals and voltage of deflections on the esophageal electrocardiogram have been shown to occur during the first week of life Some of these parallel previously reported *changes in routine* leads—e.g prolongation of P wave duration, especially during the first 35 to 60 minutes of life while others do not—e.g lower amplitude P waves in infants one hour of age or less. Widened P waves indicate left atrial enlargement, and

it is therefore of interest that left atrial pressure is not only elevated at birth, but the curve resembles that seen in adults with mitral incompetence. Sodi-Pallares & Calder [43] believe that QS complexes in leads I and aVL may also be due to left atrial dilatation. However P wave duration was not necessarily prolonged in the 9 infants with this pattern in lead I,[1] 5 of whom had it on the first day. It was not seen after the age of 53 hours.

The conventionally recorded surface P wave cannot be considered to be an optimal representation of atrial electrocardiographic activity. Moreover the value of esophageal leads in arrhythmias is dependent on considerable amplification of the atrial complex with relatively minor amplification of the ventricular complex. As P waves are small and therefore difficult to measure exactly in conventional leads [11], especially at normal standardization, this selective increase in P wave amplitude in esophageal leads could be put to good advantage if it could be shown to depend on size of, or pressure within the left atrium. This might be of special interest in the differential diagnosis of congenital heart disease or the respiratory distress syndrome because roentgenographic evaluation of size of this chamber is difficult at this age [2].

In an attempt to evaluate this, simultaneous recordings of esophageal electrocardiograms and atrial pressure recordings[2] were taken in 6 healthy infants on the first day of life. No relationship was found between P wave amplitude (Rp, Sp, largest intrinsic deflection, largest negative and positive P waves) in esophageal leads and mean atrial pressure in either the left or the right atrial chamber but the group is too small for any definite conclusion. The results of other studies relating P wave amplitude to atrial size and pressure are also conflicting. Gordon *et al.* [24], using heart specimens, found a negative correlation between P wave amplitude and left atrial volume—that is, the lower the P wave amplitude the greater the left atrial volume; while both Escobar *et al.* [21] and Testelli [46] were unable to find a relation between height of P waves in the left atrium and the left atrial pressure. Dodge & Sandler [20] also found a poor relation between left atrial volume, measured on biplane angiocardiograms, and left atrial pressure.[3] However these findings in adults may not be applicable to newborn infants.

However a number of investigations have described changes in the esophageal electrocardiogram in patients with left atrial enlargement of different etiology. According to Conte & Fusaro [14], the following criteria constitute *definite* evidence of left atrial enlargement: 1) increased area of recording of atrial leads (also noted by Benot & Rodriguez Alvarez [9]), 2) increased amplitude of the Rp wave [23, 37] and 3) increased ratio of the P R_{pi}/Q interval[4] [33]. Less certain evidence of left atrial enlargement is furnished by the following: 1) increased amplitude of the Sp wave [12] and 2) increased duration of DI ($-Q-Rp$ inter

[1] One infant also had QS in aVL.

[2] Cardiac catheterization performed by Dr R. [illegible]

[3] The size of the left atrium also does not appear to be related to the mean electrical axis of the P wave [47].

[4] P R_{pi}/Q interval: ratio of P R interval in lead II to interval from onset of atrial intrinsic deflection [illegible] ventricular esophageal Q wave.

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val) Bengtsson studying the esophageal electrocardiogram in 20 healthy children and 32 with congenital heart disease concluded that left atrial hypertrophy was generally accompanied by an increase in P wave amplitude and/or prolongation of the Q–Rp time Similar findings have been reported by Frau Wenger & Hofmann Credner and Franke

In this investigation—1) the area of recording of atrial leads is the same in both groups of infants on the first day of life and increases at the end of the week, 2) the amplitude of the Rp wave in atrial leads is lower than in adults, and 3) the ratio of the P–R_{II}/tQ intervals was not determined. However the Q–Rp time was prolonged and although the amplitude of the Sp wave was significantly lower in infants less than one hour of age the values during the week exceed those reported in children and adults Thus only their less certain criteria for left atrial enlargement are fulfilled

A relatively low amplitude Sp wave would result from either a decrease in magnitude and/or a change in direction of the mean P wave vector It does not seem to be an artefact because the same trend is seen at more than one level and the amplitude increases in younger and decreases in older infants at the end of the week An increased amount of air in the esophagus might reduce voltage although it seems more likely that older infants would have swallowed more air The distance of an electrode from the heart and the degree of pulmonary inflation are important factors influencing the P wave especially in chest leads but as the esophageal electrode lies in almost direct contiguity with the left atrium such explanations seem untenable.

On the other hand high systolic pressure in the right ventricle and low pO of the arterial blood, which are generally present after birth are usually said to be associated with an increase in amplitude of the P wave Similarly stretching of the atria an expected result of late clamping of the umbilical cord, also increases potential, either directly or by sympathetic stimulation [31] However the effects of transient atrial overload must depend not only on the size of the placental transfusion which may amount to 1/4th the total blood volume but also on which chamber is affected more. As the vector tends to shift anteriorly with right atrial enlargement and posteriorly with left atrial enlargement differentiation should be possible Recent analysis of atrial vectorcardiographic patterns accords with this view but considerable overlap is present and those authors were unable to distinguish between systolic overload (increased pressure) and diastolic overload (increased flow) [41]

Rothberger & Winterberg [39] have experimentally demonstrated that increased vagal tone decreases P wave amplitude and there is both clinical and experimental evidence that hyperpotassemia is also associated with a decrease in P wave amplitude [45 52] But the factors controlling P wave contour and amplitude are multiple and poorly understood. As Berliner & Master [7] point out no constant relation between height of P wave and degree of atrial enlargement can be expected, just as there is no constant relation between height of QRS complex and degree of ventricular enlargement However a failing heart often shows a

low voltage ventricular complex. Similarly voltage of the atrial wave must also be influenced by variations in functional status of atrial musculature. It is, therefore, not surprising that marked atrial hypertrophy is often associated with a P wave of normal amplitude.

In adults, a Q wave in infra-atrial leads which equals or exceeds 0.4 mV or 25% of the R wave in the same lead is considered suggestive of myocardial infarction [35]. However several healthy adults studied by Kistin *et al.* [28] as well as 3 infants in this series had Q waves which were abnormal by these criteria. As neither group nor individual differences in mean electrical axis were found during the first week of life, this parameter cannot account for the significant changes in amplitude of the ventricular QRS complex.

Although the incidence of arrhythmias is low in this age group the technique is well tolerated if gently carried out,[1] and it should be used in all complex cases. Whether the esophageal electrocardiogram in newborns is of value in early diagnosis of conditions primarily placing a load on the left heart still remains to be determined. The establishment of these normal standards based on a carefully selected group of healthy infants will, it is hoped, provide a sound basis for future studies.

Conclusion

Normal standards of the esophageal electrocardiogram were determined in 100 healthy infants of normal birth weight (full-term) who fulfilled the following criteria.) uncomplicated singleton delivery b) cephalic presentation, c) late clamping of the umbilical cord d) no maternal analgesia or anesthesia, and e) no known maternal illness.

These infants were serially examined—immediately after birth on the second, third and fifth or sixth days of life—and the following parameters were correlated. a) 21 to 31 gastric and esophageal leads, b) blood pressure (using xylol indicator), c) heart volume (determined on roentgenograms of the chest on the first and last examination) d) 16-lead electrocardiogram, e) phonocardiogram f) physical findings, g) age weight and length.

Statistical analysis of the data showed that multiple changes occur particularly on the first day of life, but also at the end of the week. These changes primarily affect P wave duration, and amplitude of the P wave and QRS complex. Moreover a number of relationships were found between some of the above-listed parameters.

As this is the only study of the esophageal electrocardiogram in newborns, the above-described control series of infants is considered essential for further critical evaluation of these leads. The results to date justify extension of studies—in particular to infants with circulatory problems placing a load on the left heart.

Acknowledgement

Dr John Lind, Professor and Chairman of the Department of Pediatrics, Karolinska Hospital, and Dr Charles E. Kossmann, Professor of Medicine New York University Medical Center read the manuscript and gave helpful advice. The careful technical assistance of Mrs. Siv Lundqvist is gratefully acknowledged

[1] Continuous recordings were taken in some infants during passage of the electrode. Apart from slight increase in heart rate, only an occasional premature atrial beat or slight shift in pacemaker was observed.

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SUPPLEMENT 172 1967

ACTA PÆDIATRICA SCANDINAVICA

FESTSCHRIFT IN MEMORY O[illegible]

CONSTANTIN CHOREMIS

ALMQVIST & WIKSELLS BOKTRYCKERI AB UPPSALA

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The collaborators and associates of Constantin Choremis are very grateful to all his eminent friends in Europe and the United States of America who have contributed to this Festschrift dedicated to his memory We thank them all for their eagerness to help us pay tribute to the memory of our late Professor

The editors of this volume gratefully acknowledge the valuable editorial help offered by Drs. E Apostolopoulou, C Danelatou Athanassiadou, V Kyriakidou, Th. Thomaides, C Tsenghi L. Zannos-Mariolea, D Zoumboulakis and Mr E Logan.

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CONSTANTIN CHOREMIS

(1898–1966)

The child is born from his mother womb, but it is in her embrace that he becomes human being.

Professor Constantin Choremis was born in 1898 in the mountain village of Khmenti west of Corinth. He died quite unexpectedly at the age of 68.

Choremis graduated from the Medical School of Athens University in 1921 and then went to Germany for postgraduate studies. There he worked for three years under Professor Czerny in Berlin. He was elected to the chair of Pediatrics at Athens University in 1935. In 1956–57 he served as Rector of the University and in 1957 he was elected member of the Academy of Athens. In 1959 he became President of the National Supreme Health Council.

Professor Choremis was a member of many European pediatric societies and an honorary member of British and American pediatric societies as well. He was well-known internationally having participated in a large number of international pediatric congresses.

Choremis devoted his life to the welfare of children. Throughout his career as a physician and as a university professor in all his speeches, scientific publications, and daily activities, he manifested in many ways his love and affection for his small charges.

Professor Choremis interests covered almost the whole of pediatrics: growth, blood disorders, tuberculosis, nutrition, contagious and collagen diseases, and genetics—all were subjects of investigation in the University Pediatric Clinic.

Choremis became interested in tuberculosis at the beginning of his career and kept up that interest throughout his professional life. While still in Berlin, he published a monograph on the subject which won the praise of his teacher Professor Czerny.

During the war and the German occupation, Professor Choremis concentrated on the study of the growth and general health of Athens-area children from birth to puberty. The results of this investigation, which was interrupted when Professor Choremis was imprisoned by the German authorities, were presented at the 5th International Congress of Pediatrics in New York in 1948 and gave rise to enthusiastic comments. Professor Choremis study and conclusions were widely discussed internationally and helped greatly to bring about an increase in the daily rations offered through foreign aid to the war-stricken and deprived Greek children.

After the war Professor Choremis turned again to the study of childhood tuberculosis. He and his collaborators published a total of 63 papers on this subject. A significant contribution of his was his research on the application of streptomycin in the treatment of tuberculous meningitis. His monograph on

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The child is born from his mother's womb, but it is in her embrace that he becomes a human being.

Professor Constantin Choremis was born in 1898 in the mountain village of Klimenti west of Corinth. He died quite unexpectedly at the age of 68.

Choremis graduated from the Medical School of Athens University in 1921 and then went to Germany for postgraduate studies. There he worked for three years under Professor Czerny in Berlin. He was elected to the chair of Pediatrics at Athens University in 1935. In 1956–57 he served as Rector of the University and in 1957 he was elected member of the Academy of Athens. In 1960 he became President of the National Supreme Health Council.

Professor Choremis was a member of many European pediatric societies and an honorary member of British and American pediatric societies as well. He was well known internationally having participated in a large number of international pediatric congresses.

Choremis devoted his life to the welfare of children. Throughout his career as physician and as a university professor in all his speeches, scientific publications, and daily activities, he manifested in many ways his love and affection for his small charges.

Professor Choremis' interests covered almost the whole of pediatrics: growth, blood disorders, tuberculosis, nutrition, contagious and collagen diseases, and genetics—all were subjects of investigation in the University Pediatric Clinic.

Choremis became interested in tuberculosis at the beginning of his career and kept up that interest throughout his professional life. While still in Berlin, he published a monograph on the subject which won the praise of his teacher Professor Czerny.

During the war and the German occupation, Professor Choremis concentrated on the study of the growth and general health of Athens-area children from birth to puberty. The results of this investigation, which was interrupted when Professor Choremis was imprisoned by the German authorities, were presented at the 5th International Congress of Pediatrics in New York in 1946 and gave rise to enthusiastic comments. Professor Choremis' study and conclusions were widely discussed internationally and helped greatly to bring about an increase in the daily rations offered through foreign aid to the war-stricken and deprived Greek children.

After the war Professor Choremis turned again to the study of childhood tuberculosis. He and his collaborators published a total of 63 papers on this subject. A significant contribution of his was his research on the application of streptomycin in the treatment of tuberculous meningitis. His monograph on

titled "The Results of Streptomycin Therapy in Childhood Tuberculosis" was singled out for praise by the Academy of Athens in 1948 and its author was presented with a special award.

Choremis discovered that tuberculous bacilli were often present in the CSF the bone-marrow and the liver of children with common uncomplicated primary pulmonary tuberculosis, thus proving that even in this simple form of the disease tuberculous bacilli were not confined to the lung but that bacteremia is rather common. Another important discovery was that of the bacteriophage of tuberculosis. Professor Waksman commented on the "marvelous work of the Pediatric Clinic of Athens University" when he received the Nobel Prize Award.

Professor Choremis work on hematological problems is also well known. He discovered the first focus of the sickle cell trait in Greece thus proving that it is not rare among Caucasians. During recent years he and his team studied the complications of glucose-6-phosphate dehydrogenase deficiency (favism neonatal jaundice etc.) as well as the geographical distribution of this enzyme deficiency in Greece and its relation to the hemoglobinopathies and malaria. He was invited to participate in a meeting of a WHO scientific group of nine experts on Hemoglobinopathies and Allied Disorders that was held in Genova from the 14th to the 10th of December 1965 He was elected Vice-Chairman of this meeting which reviewed the present state of knowledge on hemoglobinopathies and allied disorders, especially that of G-6-PD deficiency and prepared a report for the Director General.

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will and kind understanding and tolerance of minor human weaknesses easily won the affection of the people with whom he came in contact. He put his heart and soul into whatever he did. He worked extremely hard all his life, giving of himself without stint and in the end died in harness, leaving us much earlier than anyone expected.

There are some deaths which we mourn, but which we are able to accept as a natural end to life; there are other deaths, however which we feel are a cruel injustice. This is the feeling of all those who had come into personal contact with him, and this is especially true of his collaborators and pupils.

It was not merely those who had the good fortune to work closely with him who loved him The warm glow of his personality was such that anyone who had even the slightest share in his professional and research work would go to any length to help him. Choremis was not merely a brilliant scholar and scientist. He was above all a man of thought. His philosophical soul surveyed mankind from a high vantage point. This is why he imbued his clinic with a special atmosphere characterized not only by a searching after scientific truths, but also by high ideals and humanity None of those who worked with him can forget this atmosphere, which will continue to inspire them and enable them to carry on his work

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From the Bristol Royal Hospital for Sick Children

Recurrent Disorders in Children A Synthesis

by JOHN APLEY

Many childhood disorders come and go, only to return. Heberden [6] mentioned pains which are regularly intermittent and Samuel Gee [5] described "fitful or recurrent vomiting" But only in 1903 did Wyllie & Schlesinger [10] give a unified account of recurrent abdominal pains and vomiting with fever and headache, under the title "The periodic group of disorders in childhood and to their tetrad should now be added a fifth, diurnal limb pains [3], Mac Keith & O'Neill [7], Apley [2] and others, have emphasised that such recurrent bodily symptoms are commonly associated with emotional disturbances. A synthesis that includes both physical and emotional factors will be attempted in the discussion that follows.

As a general descriptive term I prefer *recurrent* (to course or run, again) rather than rhythmical or *periodic* (by which a regularity of intervals is understood) or cyclic (by which a constant order of events is implied). In the common syndromes of childhood a regular periodicity is not characteristic and the order of events may change So also may the components of the syndrome change the vomiting infant may become the little belly-acher in childhood and develop migraine in adult life [2].

Order is Heav'n's first law" wrote Alexander Pope the poet, and, in the quest for order the founders of western medicine tried to discern rhythms in disease. The word lunatic is a reminder that disease *rhythms* have been linked with phases of the moon. They have been linked also with mystical numbers, in the Middle Ages 7 was referred to as the Medical Number and we still hear mothers say 'He will grow out of it when he is 7 or 14 or 21 years old. Since the early days of medicine more convincing explanations for some disease rhythms have been established. In malaria the rhythm reflects the life history of the plasmodium, but such regular rhythms as that of the fever in Hodgkin's disease, in brucellosis, and occasionally in *rheumatoid* arthritis, are unexplained.

Descriptions, like that by Osler of a woman with periodic oedema recurring at intervals of 4 to 6 weeks for 74 years, linger in the memory but in practice a regular *rhythm*, a true periodicity is very uncommon. Some so-called regular rhythms are in fact irregular and many are imagined, the attempt to establish heaven's first law often goes further than the evidence warrants. For some years I have gone carefully into detail whenever

recurrent aches in the limbs and was *stunted in growth*. When eventually pseudohypoparathyroidism was diagnosed, and she was given calcium, the behaviour disorders, like the fits and pains, cleared up.

The inter-relationship of body and mind. In some of the above examples it may reasonably be held that a primary bodily disturbance was associated with emotional changes. We may recall also that influenza can be followed by depression, and that the sub-thyroid child is slow physically, mentally and emotionally. Recurrent manifestations of the epilepsies may take the form not only of fits, but also of behavioural, emotional, and occasionally somatic, disturbances; though in the epilepsies an underlying organic disorder is usually presumed, the recurrences are frequently provoked or increased by emotional stress. I summarise the history of a boy in whom severe recurrent disturbances, in the last of which he died, appeared to be provoked indiscriminately either by physical or emotional stress.

S. W. had 6 similar attacks between the ages of 13 and 35 months. In each he became irritable, listless and drowsy or comatose. He vomited, was feverish and became dehydrated; hyperglycaemia, ketosis and acidosis developed. In the last two attacks he was ataxic. On each occasion a characteristic smell was observed, eventually identified as that of butyric acid. At autopsy the only abnormality found was gliosis of the white matter including the cerebellum and brain-stem, which was considered to be a secondary phenomenon, a response to a generalised metabolic disorder. (Dr. R. P. Norman.)

The study of widespread bodily disturbances in the recurrent disorders is important in their own right, of course, but also because emotional stresses effect changes in the body largely through the endocrine and autonomic systems.

Primary emotional factors. I was long puzzled by the recurrence of episodes of severe thyrotoxicosis in a girl, until the family doctor remarked that they occurred whenever her father came home from *prison on probation!* Retention of sodium and water during periods of emotional tension, followed by a diuresis after relaxation of the tension, has been reported [8]. Again, it is recognised that exacerbation of diabetes mellitus may be provoked by emotional disturbances, which themselves may be recurrent. In such cases measurable biochemical disturbances may be demonstrated, but they are secondary to emotional disturbance.

Housman, the poet who so effectively combined lyricism and stoicism, made an interesting observation. If certain lines of poetry came into his mind while he was shaving, the hair on his face bristled so stiffly that the razor would cut them only with difficulty. We do not need the poet's piercing eye to observe many commoner examples of bodily reactions occurring with emotional stress. Blushing with embarrassment is one example, and "getting hot under the collar" with rage is another. Such everyday somatic reactions to emotions are normal; when they are excessive they may be termed psychosomatic disorders.

A large proportion of the recurrent disorders of children fulfil the criteria of psychosomatic disorder: no organic cause can be demonstrated, and there is positive evidence of an emotional disturbance, while symptoms may occur in an evident time relationship with periods of emotional stress.

I am told by his mother that Johnny's whatever-it-is comes on every month, exactly to the day and I am getting used to being disappointed.

But the important concept of recurrence remains valid for another reason—that in many instances *a pattern of disorder* can be recognised.

The Significance of Recurrence

Medicine is moving away from a pre-occupation with acute disease a preoccupation which encouraged the notion that disease is an entity a thing apart from the patient. Illness may be an aspect of living not an isolated episode with a clear beginning and end" With this approach, and with a better appreciation that symptoms and signs are reactions (sometimes maladaptive) to external or to internal stress, we are beginning to perceive some order in many of the recurrent disorders. When a pattern of illness keeps recurring we become less willing to accept it as an isolated episode and the recurrence as a series of flukes we seek to identify underlying factors which help to explain them In each individual, until the hypothesis is disproved *we should consider recurrent disorders as the intermittent expressions of persistent disorder*

The search for cause and effect may be philosophically unfashionable nowadays, but it is very useful in medical practice Though for simplicity I separate causes into internal and external groups, it should be emphasised that the two groups are often inseparable and the factors are frequently multiple Man, in health or in disease is a complex of interlocking and integrated mechanisms if we take him apart to look at them, we must remember to put him together again.

Internal factors

Primary organic factors in recurrent disorders An obvious example is recurrent urinary infection, in which an underlying *congenital* malformation of the kidney can often be demonstrated. Another is recurrent dislocation of the shoulder in which an anatomical defect (which may have been caused in the first place by injury) can be found in nearly every case

These examples are obvious because the expression of disorder is localised, when it is *not* localised a persistent underlying disorder is *more likely* to escape notice. Recurrent non localised infections are occasionally associated with a deficiency of gammaglobulin, but, as an *illustration* of the multiplicity of factors often involved, recurrent infections are much more commonly associated with poverty malnutrition or over-crowding

Order among disorder is likely to escape notice if the manifest disturbances vary from time to time. An example is polyarteritis nodosa, with recurrent but protean manifestations such as colic fever asthma anaemia neuritis. Other examples are acute porphyria with its variable episodes of paralysis, colicky pain or hysteria and gout with its somatic and emotional changes.

Such metabolic disorders are of particular interest because of the varying display of both bodily and emotional disturbances. I mention as another example a child, whose predominant disturbance had been considered to be one of behaviour though there was also a history of occasional fits and she suffered from

recurrent aches in the limbs and was stunted in growth. When eventually pseudohypoparathyroidism was diagnosed, and she was given calcium, the behaviour disorders, like the fits and pains, cleared up.

The inter relationship of body and mind In some of the above examples it may reasonably be held that a primary bodily disturbance was associated with emotional changes. We may recall also that influenza can be followed by depression, and that the sub-thyroid child is slow physically mentally and emotionally. Recurrent manifestations of the epilepsies may take the form not only of fits, but also of behavioural, emotional, and occasionally somatic, disturbances; though in the epilepsies an underlying organic disorder is usually presumed, the recurrences are frequently provoked or increased by emotional stress. I summarise the history of a boy in whom severe recurrent disturbances, in the last of which he died, appeared to be provoked indiscriminately either by physical or emotional stress.

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Such metabolic disorders are of particular interest because of the varying display of both bodily and emotional disturbances. I mention as another example a child whose predominant disturbance had been considered to be one of behaviour though there was also a history of occasional fits and she suffered from

ordinary food indigestible. In recurrent disorders I suggest that we should think in similar terms of "emotional indigestion." A combination of genetic and environmental factors often determines the type of recurrent disorder, a combination for which I have used the term "family patterning." Good health is the sum of the person's satisfactory adaptation to the total milieu, and failures in adaptation may provoke recurrent expressions of ill-health.

Changing and multiple factors

The time of an underlying, persistent disorder is emphasized by the changing stimuli that may provoke similar recurrent disturbances. The child who reacts to an allergen by developing an asthmatic attack may later react in the same way to infection, often he also learns to react in the same way to emotional stress and apparently to diminishing "doses" of stress, even when the response to allergens is insignificant and infection is absent. Because reaction patterns may become "fixed," even though the provoking factors vary, the study of the aetiology of recurrent disorders should be focussed on the earliest attacks. In later attacks additional factors may confuse and complicate the picture. I wonder whether auto-immune reactions, for example, may come to supersede those which were initiated by hypersensitivity, by infection or by emotional stress.

The realisation that provocative agents may change, and in one person may be multiple and mutually reinforcing, makes a comprehensive approach essential for the doctor.

The Comprehensive Approach

The comprehensive (or psychosomatic) approach *attempts to assess the many factors* that may be concerned in recurrent disorders. This approach *is helpful in* avoiding the errors of over-concentration by the doctor on one part or on one aspect of the person, and in appreciating that organs or *tissues have a limited repertoire* of responses, however diverse the stimuli. "A rash on the hands," it has been neatly said, "might look the same whether it be due to *Dettol*, diesel oil, distaquaine or divorce. The skin fits its owner, and it is the owner who is our patient. If, in the attempt to understand and help him, we take the person to bits for study, we should remember to put the bits together again [4].

My thesis has been that many of the recurrent disorders are intermittent expressions of persistent disorder. In the attempt to understand them we should not restrict our view to a part of the person or to an episode in his life's span. If we broaden our perspective, if we try to include *the complete person in his historical* background, we shall more nearly approach the ideal of "The whole physician for the whole patient."

This must not be taken to minimise the importance of organic causes of recurrent disorders. In children with recurrent abdominal pain an indisputable organic cause can be demonstrated in about 6 to 8 per cent [2] among which renal disease accounts for about half Of children with recurrent headache a very small proportion have a serious underlying disease of the brain or kidneys [1] which it is essential to diagnose and treat promptly But the diagnosis of an organic cause must be no less critically considered than that of an emotional or psychosomatic cause In children with recurrent headache a diagnosis of sinusitis is suspect and nearly always incorrect and most headaches considered to be due to eye strain are in fact, due to emotional strain.

In recurrent disorders the doctor who restricts his enquiries his clinical examination and his investigations to the physical aspects, is also restricting his opportunities of helping the child who has been brought to him Organic disease should be diagnosed or excluded promptly but there should be no wantonness in inquiry' in case the physician becomes a pathogenic agent in perpetuating illness by his well meaning but never-ending efforts to find a physical cause [9]

External factors

A mysterious aspect of many recurrent disorders is not so much that the symptoms come but that they come and then go Why is the pain associated with hydronephrosis often recurrent rather than permanent? Why is acute recurrent porphyria not chronic porphyria? Why do little bellyachers have abdominal pain only at times?—though these episodes may be predictable Why do so many physical and psychogenic disorders, like volcanoes, erupt only occasionally? We know only a little about the compensating mechanisms that attempt to maintain or restore the homeostasis of body and mind, but it is clear that external agents can transform a potential internal weakness into actuality bring to light from time to time a disorder that was hidden, or provoke exacerbations. The environment in which we live and to which we are continually adapting is not exclusively physical but also emotional and social and the reactions of a person to the environment are excited not only through physical media but also through the mind.

In some instances the recurrence of disorder in the child merely reflects the recurrence of an outside stimulus, in the home school or social environment An example is the girl with thyrotoxicosis previously mentioned. Another is that of a boy who had severe abdominal pain with marked pallor each time his mother took him by car to his boarding school at the start of a school term On one occasion, when she drove him to school during the summer vacation to collect his cricket bat he had no pain In some children recurrent disorders can be linked with occasions on which they are unduly excited. recurrent vomiting or asthma often occurs at Christmas or other parties, or on birthdays or at the start of school term

When a patient suffers from recurrent indigestion we need to enquire about dietary indiscretions we appreciate that he may have eaten something which could upset any stomach but we appreciate also that he may have some internal disorder inborn or acquired, which makes even

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From the Department of Pediatrics, New York University School of Medicine

Developmental Hyperactivity

by HARRY BAKWIN

Developmental Hyperactivity

Developmental disorders account for many of the everyday problems in children. Those which influence behavior relate principally to the control of motility and the acquisition and proper use of the language functions. Enuresis may also be included in this category.

The developmental disorders are inborn deviations in the organization of cerebral function. The clinical manifestations simulate those produced by cerebral lesions, but no changes in the brain can be found. There are no characteristic electroencephalographic patterns.

The disorders are interrelated and familial. Any combination is possible in the individual and the family. Delayed development of speech, specific reading disability (developmental dyslexia) and spelling disability are frequently observed in the same individual. It is common to find that the father of a child with developmental dyslexia is a slow reader and poor speller.

Boys are affected much more often than girls. There is no relation to the intellectual status, the economic status, race or ethnic origin. A severe emotional reaction may accompany the disorder and dominate the clinical picture.

Spontaneous improvement takes place during adolescence. In some instances the improvement is complete and here one may speak of a developmental delay. Some children are not ready to read until they are 8 or 10 years of age [1]. They then start to read and catch up to their age peers quickly. In others improvement takes place but the deviation persists throughout life, although in attenuated form.

The developmental disorders of motility include delay in beginning to walk, abnormal clumsiness, alterations in lateral dominance and hyperactivity.

Symptoms

Hyperactivity of a degree sufficient to create a problem at home and in school, is a frequent complaint voiced by parents [2, 3]. The symptom is often noticed during infancy. Mothers complain that they have difficulty holding the infant, that he seems to want to spring out of their arms, that he will not remain in the play pen. Occasionally the hyperactivity is not observed until later, anywhere up to 6 years according to Laufer & Denhoff [2]. The hyperactivity may not present a serious problem until the child enters school and is expected to sit still there.

The hyperactive child is continually on the move, rushing about from morning

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The hyperactive child is continually on the move, rushing about from morning

until night without let-up. He is uncom fortable when quiet He plays harder and with more zest than his peers and seems to enjoy himself more. He continually explores his environment he takes his toys apart he annoys his parents and play mates. Parents describe him as wound up and in perpetual motion

A number of other behavioral symptoms frequently accompany the hyper activity—distractibility or difficulty in concentrating short attention span, vari able performance of school work, excellent one day poor the next; impulsiveness, that is, acting without premeditation, low frustration level or impatience

The short attention span and distractibility may interfere seriously with school performance The child s attention cannot be sustained long enough for him to listen to the teacher s questions, assignments and other classroom work and consequently his work suffers Many however do well at school

The children are often considered clumsy because they cannot manage buttons and the like and because they are destructive Actually they are frequently unusually agile at climbing trees and the like Their apparent clumsiness is due to haste, impatience and a low frustration level

In some children the speech is rapid, hurried and difficultly understandable The child is in a hurry with his speech as with his other activities. Occasionally there is cluttering speech another devel opmental disorder

Another type of hyperactivity is also frequently met with in children This con sists of a general restlessness, a continual swinging of the leg difficulty in sitting still squirming It is unaccompanied by the other symptoms of the hyperactivity syndrome

Despite their exasperating behavior children with the hyperactivity syndrome are often kind obliging and eager to please The schoolage children become aware of the undesirability of their behavior and are concerned.

Parents find the hyperactive child diffi cult to manage The natural parental affec tion is repeatedly challenged by behavioral difficulties at home in the neighborhood and at school Sooner or later hostile parental attitudes emerge to which the child reacts by an intensification of the hyperactivity and other behavioral distur bances.

Specific learning difficulties often ac company the hyperactivity [4] The chil dren have been found to be inferior to control children in visual motor skills perceptual speed level of sensory motor development and attentiveness. They tend to respond to wrong cues and fail to respond to correct ones. In addition they have difficulty in processing auditory in formation. A slow diffuse dysrhythmia in the electroencephalogram was found in about half the cases studied by Werry and co-workers [5] Its significance is not clear As possible causes they suggest a matura tional disorder a psychophysical effect and brain damage

Hyperactivity is about 4 times as com mon in boys as in girls It i ompatible with a high order of intelligence There are no data on family incidence

Differential Diagno i

The hyperactivity is cons i l to be developmental when a histor f rebral

damage and neurologic signs is absent. It is by far the most frequent type of hyperactivity seen in children. The wide variability in children's activity has already been observed shortly after birth [6, 7, 8]. In a study of infants during the first 2 weeks of life Irwin [6] found that the most active infant in his group was almost 300 times as active as the least active one. It is conceivable that developmentally hyperactive children represent a group which falls at the upper end of a normal curve of variability but this appears unlikely since the group seems sharply demarcated.

A history of difficult labor is of doubtful significance in infants born at term. Full-term infants tolerate anoxia well. Fraser and Wilks [9] followed 60 infants with severe neonatal anoxia. None developed hyperactivity later on. Minde & Webb [10] compared the birth histories of 56 hyperactive children with a similar number of controls. They conclude that "the hypothesis that chronic hyperactivity is frequently the result of complications of pregnancy and delivery receives little support from this study."

Cerebral damage as a cause of the hyperactivity is suspected when there is a history of cerebral injury or disease and when neurologic signs are present. Infants born prematurely, especially the smaller ones, and infants born to mothers who bled during pregnancy or who were toxemic often show neurologic and behavioral sequelae [11]. The hyperactivity in children with cerebral damage has the same character as that seen in developmental hyperactivity but it is ordinarily more intense.

Hyperactivity is often a prominent symptom in children with reactive behavioral disorders. The hyperactivity appears later than in the case of developmental hyperactivity or cerebral damage; it is less intense and not as continuous, being interspersed with periods of quiescence. It is ordinarily not associated with distractibility and short attention span. Usually emotionally disturbing circumstances are present in the home or school.

Early infantile autism. Aside from the fact that children with the hyperactivity syndrome, in contrast to autistic children, relate well to persons, the hyperactivity in children with early infantile autism is distinctive and readily distinguishable from other types of hyperactivity. The movements of the autistic child are rhythmic, repetitious and purposeless—a back and forth pacing, a whirling, a body rocking. The movements are often accompanied by a flapping of the hands and bizarre movements of the fingers. The periods of activity are interspersed with periods of inactivity when the child will sit quietly for long periods watching a revolving phonograph or fan or looking off into space as though deep in thought.

Children with hyperthyroidism are usually overactive. The diagnosis is suspected when the clinical manifestations of hyperthyroidism are present—exophthalmos, palpable thyroid, excessive sweating, rapid pulse and weight loss.

Prognosis

The condition is self limited. The excessive activity usually subsides during early adolescence, occasionally earlier. It has been observed up to 18 years. The other manifestations may persist but are better controlled.

until night without let-up He is uncomfortable when quiet. He plays harder and with more zest than his peers and seems to enjoy himself more He continually explores his environment he takes his toys apart he annoys his parents and playmates. Parents describe him as 'wound up and in perpetual motion

A number of other behavioral symptoms frequently accompany the hyperactivity—distractibility or difficulty in concentrating short attention span variable performance of school work excellent one day poor the next, impulsiveness, that is, acting without premeditation low frustration level or impatience

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Hyperactivity is about 4 times as common in boys as in girls. It is compatible with a high order of intelligence There are no data on family incidence

Differential Diagnosis

The hyperactivity is considered to be developmental when a history of cerebral

A number of unfavorable side-effects accompany amphetamine administration. A temporary loss of appetite and poor sleep are not infrequent. Sometimes the children acquire a pale, pinched, serious expression with hollows under the eyes. Bad taste in the mouth and fetor oris may also be present. These are generally not sufficient reasons for stopping medication.

Indications to discontinue the drug are exaggeration of the symptoms of the hyperactivity syndrome, epigastric pain, headache and finger tremors.

The drug is given for 8 weeks and then gradually tapered off. The improved behavior during this time helps to resolve conflicts at home and at school, thereby lessening the secondary factors which ordinarily increase the symptoms.

If the symptoms recur the drug may be given again.

Deanol (Deaner) in graded doses starting with 25 mg once a day and increasing to 100 mg, if necessary *is also effective.* It has no known adverse effects.

Chlorpromazine is effective in some cases [13]. It must be given in adequate dosage. For a child 6 years and over an initial dose is 20 mg (2 teaspoons of the syrup of thorazine) 3 times a day. The dose is increased to 150 mg a day if necessary. The parents should be warned that the child may be sleepy for a day or two after the drug is introduced. This wears off quickly.

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Management

The first step is an explanation to the parents of the nature of the deviant behavior If possible both parents should be present They should be told that the excessive activity is an inborn characteristic and that it is not wilful misbehavior Asking the parents at this point to enumerate the youngster s favorable qualities serves to emphasize to them that, despite his frequently exasperating behavior their child is basically a good youngster

The parents are told, further that the child s behavioral symptoms are not due to their mismanagement Parents tend to blame themselves for any aberration in their child s behavior It is a great source of comfort for them to have an explanation of the true nature of the behavioral deviation and to be relieved of feelings of guilt and inadequacy The parents are further told about the favorable outcome.

The family situation should be reviewed and corrective suggestions made as indicated. Nagging injunctions to sit still and punishments are useless. Parental conflicts about management should be clarified. A well-ordered routine with a minimum of distractions helps greatly to reduce confusion.

Some hyperactive children do better in a progressive school where freedom of movement is permitted. For most, however a strict regimen with clear-cut rules and definite assignments is preferable Since the attention span is short the assigned tasks should be short enough so that they can be completed. Concrete tasks are better handled than abstract ones.

To minimize distractions classrooms should be void of pictures on the walls and clocks. Window curtains should be drawn. Seats should be widely spaced.

The diagnosis of minimal cerebral damage has become a popular one and psychologists are labelling hyperactive children in this way much too freely This diagnosis is naturally highly distasteful to parents. Although the criteria for a diagnosis of developmental hyperactivity are not as precise as one would like in the absence of a definite history of cerebral injury and in the absence of neurologic signs, parents should be told that there is no reason to suspect cerebral damage

Medication , Amphetamine introduced by Bradley [12] is generally regarded as specific for the treatment of the hyperactivity syndrome whether due to a developmental disorder or cerebral damage A favorable response is regarded by many as supportive evidence for either of these diagnoses [2] A prompt reduction in activity and a better sustained attention span may be expected

The amphetamines are available in two forms, the racemic form (benzedrine sulfate) and as dextro-amphetamine (dexedrine) In some children one form is effective and not the other in others both forms are equally effective The dosage of dexedrine is about half that of benzedrine

As an initial dose for children 6 years and older 10 mg of benzedrine or 5 mg of dexedrine is given after breakfast The dose is increased if necessary every 2 or 3 days until a therapeutic or toxic effect is produced. A clinical effect is observed in 20 to 30 minutes. A second dose later on the day may be given if the early favorable effect wears off Dexedrine is available in spansule form which permits gradual release of the drug

Methämoglobin rasch reduzierten und Zellen, die das nicht tun.

Bereits auf dem Internationalen Hämatologenkongreß in Stockholm 1964 wurden jedoch Zweifel laut, ob mit der zytologischen Methodik das hypothetische Zellmosaik sichtbar gemacht wird [7–10]. Frischer *et al.* [7] fanden bei sorgfältigen Verlaufskontrollen der Reduktion in Anwesenheit von Methylenblau und Glukose je nach dem Zeitpunkt der Prüfung ein anderes Verhältnis von reduzierenden und nichtreduzierenden Zellen, ein Ergebnis, das der Auffassung von zwei definierten Zellpopulationen widerspricht. Wir entschlossen uns daher, dieser Frage in erneuten Untersuchungen nachzugehen.

Methodik

Als Basis für die Versuche benutzten wir den Brewer-Test [4]: 2 ml Citratblut werden mit 0,1 ml 1,25% Natriumnitrit, 0,1 ml 0,5 10^{-3} mol Methylenblau und 0,1 ml 5% Glukose versetzt und bei 37° inkubiert. Zu verschiedenen Zeiten wurden Proben zur zytologischen Untersuchung und Methämoglobinbestimmung entnommen. Die Originalanweisung von Brewer *et al.* [4] wurde je nach dem Untersuchungszweck gelegentlich modifiziert. Für eine Anzahl Versuche wurde statt Methylenblau eine äquimolare Lösung von Nilblausulfat verwendet.

Die *Methämoglobinbestimmung* wurde nach Evelyn und Malloy [6] durchgeführt; in jedem Fall wurden die Erythrozyten vor der Hämolyse gewaschen. Der zytologische *Methämoglobinnachweis* erfolgte nach Kleihauer und Betke [8].

Als *Träger des G-6-PD-Mangels* standen uns einige Patienten unserer Klinik zur Verfügung. Ob es sich um Kinder italienischer und griechischer Abstammung handelt. In allen Fällen lag die "kaukasische Variante" des G-6-PD-Mangels mit praktisch völlig fehlender Enzymaktivität bei den männlichen Probanden vor. Die Mütter erwiesen sich nach dem Ergebnis der Enzymbestimmung als heterozygot. Außerdem verdanken wir Herrn Professor Waller die Möglichkeit, daß wir Untersuchungen an Mitgliedern einer deutschen *Familie mit G-6-PD-Mangel* durchführen konnten.

Ergebnisse

Methämoglobinbildung im Brewer-test [4]. *Nach Zusatz* der Reagenzien erfolgte in sämtlichen Blutproben eine rasche Methämoglobinbildung (Abb. 1). Bei normalen *Versuchspersonen* war nach 40–60 Minuten das Maximum erreicht mit Werten zwischen 0–90%. Methämoglobin. Heterozygote *Frauen* verhielten sich ähnlich, erreichten aber meist einen etwas höheren Maximalwert und etwas später als die *Kontrollen. Bei hemizygoten Jungen stieg* der Wert noch bis zur dritten Stunde an und verblieb dann auf einer Höhe zwischen 97 und 100%.

In zwei Versuchen wurde Nitrit 15 Minuten vor Zusatz von Glukose und Methylenblau in das Blut eingebracht. Dies änderte am Ablauf der Oxydation nicht viel.

Ablauf der Methämoglobinreduktion. Bei den Kontrollen erfolgte die Methämoglobinreduktion in ihrem Hauptanteil in der zweiten Stunde und *führte mit dem* Ablauf von drei Stunden zu Werten unter 10% Methämoglobin (Abb. 1 und 2). Bei hemizygoten Jungen blieb der *Methämoglobinwert* über viele Stunden unverändert in der Nähe von 100%. Die heterozygoten Frauen verhielten sich intermediär, *zeigten* aber erhebliche Unterschiede in der Reduktionsgeschwindigkeit (Abb. 2). Eine künstliche Mischung von normalen Erythrozyten und Erythrozyten eines hemizygoten Pa-

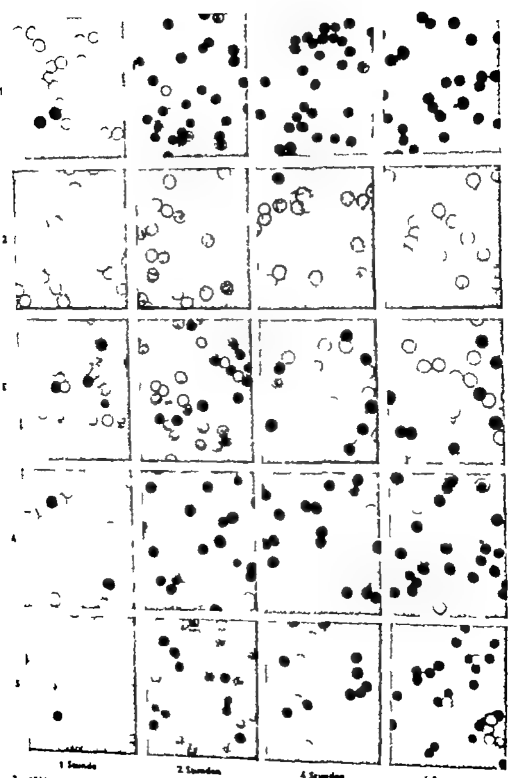
Aus der Univ Kinderklinik Tübingen Direktor Prof Dr K. Betke

Zytologische Untersuchungen zur Frage des Zellmosaiks bei heterozygoten Frauen mit Glukose 6 Phosphatdehydrogenase Mangel

von K. BETKE, E. KLEIHAUER und Z. KNOTEK

Bei Glukose-6-Phosphatdehydrogenase (G-6-PD)-Mangel ist es schwierig Heterozygote sicher zu erfassen Da es sich um ein X chromosomal vererbtes Leiden handelt kommen nur Frauen als Heterozygote in Frage. Die Enzymaktivität weist bei solchen Personen erfahrungsgemäß eine *große Schwankungsbreite* auf. Der für Screening Untersuchungen so wertvolle Motulsky Farbtest ist in dieser Beziehung unzuverlässig aber auch die spektrophotometrische Messung der Enzymaktivität läßt häufig im Stich Zu dieser Frage wurde von Choremis *et al* [6] ein großes und aufschlußreiches Material geliefert. In einer breit angelegten Untersuchung fanden sie *bei 49 Müttern* von hemizygoten Jungen, also bei mutmaßlich heterozygoten Frauen, Enzymaktivitäten von Null bis nahe an die untere Grenze der Norm Im Einzelfall war es oft unmöglich zu entscheiden, ob eine Mutter homo- oder heterozygot war während — im Gegensatz zu den Verhältnissen beim G 6-PD Mangel der Neger — die Abgrenzung von heterozygoten Frauen gegen Gesunde weniger schwierig war

Eine interessante neue Möglichkeit zur Untersuchung heterozygoter Frauen ergibt sich aus zytologischen Studien. Wenn die von Lyon *aufgestellte* Hypothese zutrifft, *müßten bei heterozygoten* Frauen mit G 6-PD-Mangel *zwei* Erythrozytenpopulationen vorliegen. erstens Erythrozyten *mit normaler Enzymaktivität* zweitens Erythrozyten mit voll ausgeprägtem Defekt. Dies wurde bereits 1962 von Beutler *et al* [3] wahrscheinlich gemacht, indem sie fanden daß die intrazelluläre Reduktion von Methämoglobin in Gegenwart von Methylenblau und Glukose (wofür G-6-PD erforderlich ist) bei heterozygoten Frauen mit G-6-PD Mangel nicht wie in einer einheitlichen Zellsuspension ablief sondern die Existenz zweier verschiedener Zellpopulationen nahelegte Durch die von Kleihauer und Betke [8] entwickelte Methode, Methämoglobin in Erythrozyten eines Blutausstriches zytologisch *nachzuweisen* wurde es möglich dieser Frage direkt nachzugehen. Unabhängig voneinander stellten *Sansone et al [11] und* Tönz und Rossi [13] solche Untersuchungen an und zeigten daß in der Tat bei der Methämoglobinreduktion in Anwesenheit von Glukose und Methylenblau bei heterozygoten Frauen zwei Populationen von Erythrozyten auftraten Z[illegible] die


1
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4 Stunden

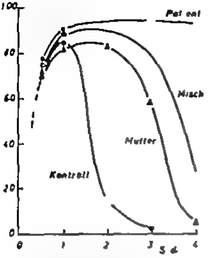


Abb. 1. Methämoglobinbildung und Methämoglobinreduktion im Brewer-Test. Eine künstliche Mischung von Blut des hemizygoten Patienten mit Kontrollblut verhält sich ähnlich wie das Blut der heterozygoten Mutter

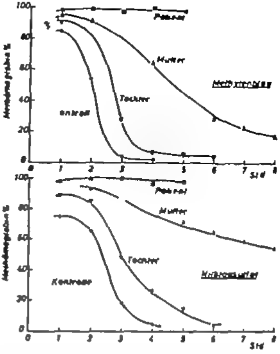


Abb. 2. Methämoglobinreduktion im modifizierten BREWER-Test. Die Mutter und Tochter des hemizygoten Probanden sind beide heterozygot (Familie von Waller et al. 1966). Versuchsbedingungen: 2 ml Citratblut + 0,1 ml 1,5% Natriumnitrit; nach 15 Minuten Zusatz von 4,0 ml Kochsalz-Phosphat pH 7,0, 0,3 ml 1 · 10⁻⁴ mol Methylenblau oder Nilblausulfat, 0,3 ml 5% Glucose. 37°, O_2-Atmosphäre durchschüttelt in.

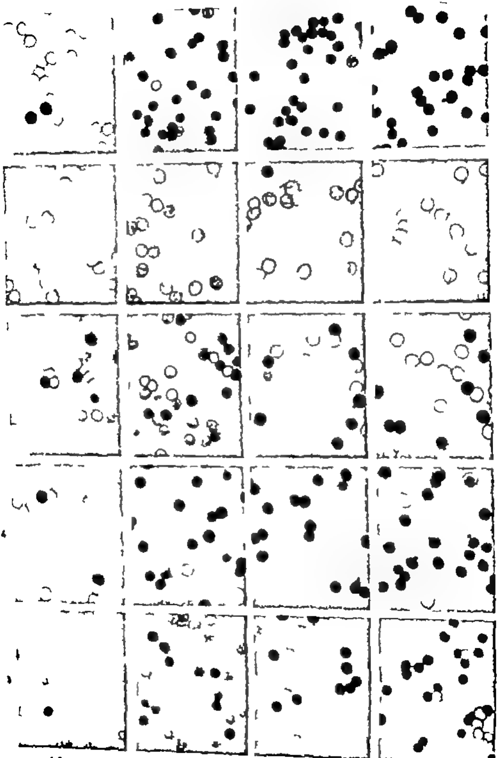
tienten zeigte prinzipiell den gleichen Reduktionsablauf wie Erythrozyten einer heterozygoten Frau (Abb. 1). Eine zweiphasische Kurve, wie man sie an sich hätte erwarten können, war nicht zu erkennen.

Wurde Nilblausulfat statt Methylenblau verwendet, verlief die Reduktion insgesamt etwas langsamer. Abgesehen davon war jedoch kein grundsätzlicher Unterschied gegenüber den Verhältnissen mit Methylenblau zu erkennen (Abb. 2).

Einige Blutproben wurden zunächst mit Nitrit behandelt, nach Methämoglobinbildung auf der Zentrifuge gewaschen und anschließend mit Glukose und Methylenblau inkubiert. Die Reduktion verlief in diesen Ansätzen wesentlich schneller als in Ansätzen mit Anwesenheit von Nitrit, wie es dem Brewer-Test entspricht. Auch hemizygote Jungen zeigten eine langsame, aber eindeutige Reduktion. Weder bei heterozygoten Frauen noch in Mischungen konnte eine zweiphasische Kurve festgestellt werden.

Zytologische Ergebnisse. Bei der verwendeten Methode wird aus Erythrozyten, die Methämoglobin enthalten, der Blutfarbstoff herausgelöst, während Erythrozyten mit Oxyhämoglobin (bzw. reduziertem Hämoglobin oder auch Carboxyhämoglobin) ihren Farbstoff behalten. Leere Zellen sind also gleichbedeutend mit Methämoglobin-Zellen, volle Zellen gleichbedeutend mit Oxyhämoglobin-Erythrozyten.

In Blutproben von *Normalpersonen* fanden sich im Brewer-Test mit Methylenblau auf der Höhe der Methämoglobinbildung



1
2
3
4
5

1 Stunde

nach 1 Stunde überwiegend Methämoglobin-Zellen, also leere Stromata; in jedem Fall aber auch einige volle Zellen und einige Intermediärformen, von denen man annehmen muß, daß in ihnen der Blutfarbstoff nur teilweise in Methämoglobin umgewandelt ist. Nach 2 Stunden war die Hälfte der Zellen oder mehr voll, ein Teil intermediär, der Rest leer. Nach 3 Stunden lag abgesehen von vereinzelten leeren oder intermediären Zellen eine einheitliche Population von vollen, also Oxyhämoglobin-Zellen vor. Wurde statt Methylenblau Nilblausulfat verwendet (Abb. 3), dann war der Verlauf etwas langsamer. In diesem Fall waren nach 4 Stunden mit vereinzelten Ausnahmen alle Zellen voll.

Hemizygote Jungen hatten nach 1 Stunde gelegentlich noch einzelne volle Zellen, spätestens nach 2 Stunden war jedoch eine einheitliche Population von leeren Zellen, also Methämoglobin-Zellen vorhanden. Dies blieb über viele Stunden unverändert so. Eine einzelne Oxyhämoglobin-Zelle konnte jedoch gelegentlich gesehen werden (Abb. 3, 5 Stunden). Mit Nilblausulfat wurden die gleichen Resultate erzielt wie mit Methylenblau.

Heterozygote Frauen hatten ähnlich wie Normalpersonen nach 1 Stunde neben leeren Zellen stets auch einige volle Zellen. Im Ablauf der Reduktion mit Methylenblau vermehrten sich die vollen Zellen, jedoch nicht so schnell wie bei den normalen Kontrollen. Auch intermediäre Zellformen wurden gesehen. Die Relation von vollen zu leeren Zellen verschob sich langsam zugunsten der vollen Zellen. Nach 5–6 Stunden waren die leeren Zellen verschwunden oder nur noch in geringer Zahl vorhanden. Bei Verwendung von Nilblausulfat (Abb. 3) war der Ablauf insofern etwas anders, als sich das nach 2–3 Stunden erreichte Verhältnis von vollen zu leeren Zellen über weitere 2–3 Stunden annähernd konstant hielt. Auch hier traten intermediäre Zellformen auf und es sank schließlich auch die Zahl der leeren Zellen. Dies war vor allem dann deutlich, wenn von vornherein die Zahl der vollen Zellen rascher zugenommen hatte (Abb. 3, Serie der Tochter).

Künstliche Mischungen aus Erythrozyten von hemizygoten Jungen und Normalerythrozyten verhielten sich ebenso wie Erythrozyten von heterozygoten Frauen. Auch in diesem Fall nahm im Lauf der

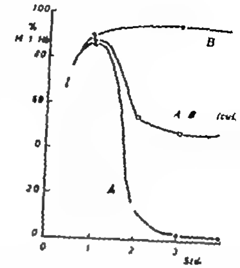


Abb. 4. Errechneter Verlauf der Methämoglobinreduktion in einer künstlichen Mischung (A + B) von Normalblut (A) mit Blut eines Hemizygoten (B), wenn die beiden Erythrozytenpopulationen unabhängig voneinander reagieren. Vergleiche hiermit den tatsächlichen Verlauf in Abb. 1

Abb. 3. Zytologische Befunde im Ablauf des modifizierten Brewer-Testes über 6 Stunden. Von oben nach unten: 1 = Normaler Erwachsener, 2 = Hemizygoter Mann (Patient von Prof. W. Keller), 3 = Mutter von 2, heterozygot, 4 = Tochter von 3, heterozygot, 5 = Künstliche Mischung von 1 und 2. — Versuchsbedingungen wie in Abb. 2

Inkubation die Zahl der vollen Zellen zu und die der leeren Zellen ab, und es traten auch intermediäre Zellen auf. Mit Nilblausulfat wurde das Bild von zwei Zellpopulationen länger aufrecht erhalten als mit Methylenblau (Abb. 3).

Besprechung

Was erwartet man von einem Zellmosaik mit zwei Populationen von Erythrozyten, aktiven und inaktiven, bei der Reduktion im Brewer-Test? Wenn beide Erythrozytenarten ohne gegenseitige Beeinflussung reagieren, mußte die in Abbildung 4 gezeichnete Kurve resultieren: eine Reduktion bis auf einen mittleren Methämoglobinwert und dann ein Verharren auf dieser Höhe. Die tatsächlichen Versuchsergebnisse liefern nie solche Kurven (vgl. Abb. 4 mit Abb. 1). Dies zeigten bereits Beutler und Baluda [2] 1963 für die Reduktion mit Methylenblau und Glukose nach Auswaschen von Nitrit.

Da die Reduktion weiterläuft, als man erwarten sollte, muß man annehmen, daß die normalen Erythrozyten den defekten Erythrozyten eine Stoffwechselhilfe leisten. Nach Untersuchungen von Banaschak und Schaler [1] sowie von Beutler und Baluda [ ] ist es sehr wahrscheinlich, daß Leukomethylenblau der Mediator ist. Wenn die normalen Zellen mit Hilfe des Methylenblau-Leukomethylenblau-Wechsels ihr eigenes Methämoglobin reduziert haben, fahren sie fort, Leukomethylenblau zu bilden, welches dann den defekten Zellen als Reduktionsmittel zur Verfügung steht. So kann man sich den Mechanismus vorstellen.

Wir haben versucht, dieser „Stoffwechselhilfe“ dadurch entgegenzuwirken, daß wir die Reaktion in reiner O_2-Atmosphäre unter ständigem Durchmischen der Blutprobe und mit verdünnten Ansätzen durchführten. Durch Sauerstoff und Verlängerung des Weges von einem zum anderen Erythrozyten sollte Leukomethylenblau oxydiert werden, bevor es einen anderen Erythrozyten erreicht. Einen eindeutigen Effekt konnten wir jedoch nicht feststellen.

Entsprechend dem Verhalten der Methämoglobinwerte verschwinden auch in der zytologischen Auswertung bei längerer Dauer die „leeren“ Zellen in Mischungen von defekten und normalen Zellen. Wenn die beiden Erythrozytenpopulationen voneinander unabhängig wären, mußte man nach 3–4 Stunden ein stabiles Verhältnis von „leeren“ zu „vollen“ Zellen haben, und es dürften auch keine intermediären Zellformen in größerer Zahl auftreten. Die tatsächlichen Befunde sind wie berichtet anders. Das zytologische Bild nach 4 oder 5 Stunden zeigt also nicht exakt das Verhältnis von normalen zu defekten Zellen an. Zwar darf man annehmen, daß Zellen, die nach 5 Stunden „leer“ sind, keine G-6-PD-Aktivität besitzen, doch sind unter den „vollen“ Zellen nicht nur normal aktive Zellen, sondern zweifellos auch einige defekte Zellen, denen geholfen wurde.

Beutler und Baluda [2] hatten festgestellt, daß bei Verwendung von Nilblausulfat anstelle von Methylenblau der Effekt der Stoffwechselhilfe nicht auftritt. Dies können wir nicht bestätigen, wenn wir die Methämoglobinwerte betrachten (Abb. 2). Auch in diesem Fall läuft die Reduktion weiter, allerdings langsamer als bei Verwendung von Methylenblau. In der zytologischen Auswertung fanden wir jedoch eine gewisse Stabilität von zwei Populationen über ~ bis 3 Stunden (Abb. 3).

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La valeur des différents BCG

par ROBERT DEBRÉ

La valeur du vaccin BCG comme agent de protection contre la tuberculose est acquise aujourd'hui après des discussions passionnées et des études prolongées. Il va de soi que ce vaccin, pas plus qu'aucun autre, ne protège tous les sujets vaccinés sans exception, encore que nous ne sachions pas exactement les causes de ces défaillances vraies de la vaccination. Celle-ci protège généralement contre les manifestations de la tuberculose primaire, la tuberculose miliaire, la méningite tuberculeuse, la pleurésie tuberculeuse, la tuberculose pulmonaire progressive précoce et même semble-t-il, la tuberculose pulmonaire tardive. Sur ces points le Professeur A. Wallgren a rapporté les conclusions de son expérience et montré les limites de notre connaissance dans un intéressant document présenté à la Réunion de la Commission de Prophylaxie de l'Union Internationale contre la Tuberculose à Munich en 1966*.

Mais on n'observe que trop de fausses défaillances: deux sont importantes. La première est liée à une contamination tuberculeuse peu de temps avant ou peu de temps après la vaccination, cette dernière ne peut en empêcher ou en modifier l'évolution. D'autres fausses défaillances du BCG sont liées à une faute dans l'administration de celui-ci, comme par exemple l'exposition à la lumière solaire. Mais la cause de défaillance vraie la plus importante réside dans l'emploi d'un vaccin de médiocre qualité. C'est qu'en effet il n'y a pas actuellement un vaccin BCG mais plusieurs et ils diffèrent entre eux car les souches-filles, toutes issues de la souche Nocard modifiée par Calmette et Guérin, diffèrent entre elles. Sans doute l'innocuité de toutes est reconnue mais leur valeur varie. C'est lorsque furent étudiés les résultats des campagnes de masse entreprises aussitôt après la fin de la deuxième guerre mondiale par les Croix Rouge scandinaves puis l'UNICEF et ensuite l'OMS, que l'on vit des variations dans le degré de l'allergie conférée, que celles-ci étaient très importantes suivant les zones considérées et que leurs causes étaient sans doute multiples et en grande partie liées aux conditions de transport et d'emploi des ampoules. Mais on dut bientôt convenir que jouait aussi l'activité inégale des vaccins issus des divers centres de fabrication, voire des lots successifs provenant d'un même laboratoire [Robert Debré et R. Mande].

Dans le même temps, des travaux expérimentaux mettaient en lumière les variations du BCG. On savait qu'il n'y avait pas et sans doute n'y avait jamais eu la parfaite homogénéité d'une souche

* Bulletin de l'Union Internationale contre la Tuberculose. Vol. XXXVIII, n° 1 juin 1966, p. 7

issue d un seul clone La possibilité de dissociation artificielle du BCG en types R et S avait depuis longtemps été mise en lumière dans le laboratoire même de Calmette [A. Saenz et L. Costil K. Birkhaug] Cette dissociation ne légitimait aucunement la crainte d un retour à la virulence Elle n en était pas moins réelle et représente comme l annonce des travaux ultérieurs sur les différences entre les cultures de BCG entretenues dans les laboratoires variés et des recherches sur les divers types de colonies qui coexistent dans la même culture

En 1946 K. A. Jensen, ayant obtenu par la mesure de la lésion locale du cobaye des résultats différents avec deux échantillons de BCG conclut à une inégalité de virulence entre eux. Mais cette assertion fut contestée et l individualisation de « sous-souches » ou « souches-filles » à caractères séparés ne fut réellement acquise qu à la suite des publications de R Dubos et de ses collaborateurs. Ceux ci montrèrent que les diverses souches-filles n ont pas toutes le même pouvoir immunisant. Même lorsque les caractères étudiés sont sans rapport connu avec l efficacité du vaccin. Les preuves qu elles apportent des différences entre les BCG méritent d être retenues. Mais ce qui compte le plus est actuellement le retentissement sur l activité des vaccins des caractères de chaque souche fille Il ne fut pas admis sans débat. On trouvera dans la monographie de A. Frappier et M. Panisset l exposé des discussions auxquelles la question donna lieu jusqu en 1958 [Monographie de l Institut de Microbiologie de l Université de Montréal Canada, 1957].

Par ailleurs comme R Dubos le faisait observer dès 1949 les suspensions de BCG utilisées pour les vaccinations sont très inégalement riches en unités vivantes. On se rendait ainsi compte peu à peu qu'il restait beaucoup à faire pour rendre la production de BCG plus constante et régulière dans son efficacité. La lyophilisation, proposée en 1944 par A. Leschinskaia ouvre une voie fort importante à cet égard Mais les progrès qu elle autorise risquent de rester incertains si l on n arrive pas à éprouver les vaccins sous la forme même où ils sont administrés à l homme Les recherches à ce sujet sont menées tout d abord dans des laboratoires adonnés chacun au contrôle de sa propre production L étude réalisée à Bergen par E. Krohn [1952] mérite une mention particulière De leur côté K Bikhaug, O Sievers, Orakov et Engback entre autres, s attachent à la description des épreuves qu ils considèrent comme des plus utiles. Des travaux similaires sont entrepris par les auteurs soucieux d évaluer les procédés de lyophilisation qu ils mettaient au point. Parmi eux on signale ceux de T Ebina A. Frappier H Frappier H Humabe et T Sawada Y Obayashi, J Aronson et P Schneider S R Rosenthal J Ungar et coll

Au fur et à mesure que se développent ces investigations, les épreuves proposées se multiplient Tout en consacrant leurs efforts aux comptes d unités vivantes, beaucoup essaient de développer d autres techniques *in vitro* En outre la vérification de l activité des vaccins chez l animal est de plus en plus employée en s inspirant en premier lieu des méthodes qui avaient servi à Calmette Boquet, Nègre et coll dans leurs études fondamentales. L observation des sujets vaccinés n en garde pas

moins sa place et fait encore l'objet de nombreux travaux [R. Mande et A. Huet].

On peut s'étonner alors que l'inégalité possible entre vaccins commence à être reconnue, que les épreuves mises en pratique dans les laboratoires de production ne soient pas rapidement appliquées à l'évaluation simultanée de vaccins d'origines multiples. Mais de telles comparaisons, pour se montrer fructueuses, sont plus difficiles à réaliser que la surveillance d'un type de BCG déterminé et de ses variantes.

Cependant nous nous sommes demandé avec nos collaborateurs s'il n'y avait pas moyen d'éprouver les vaccins en utilisant conjointement l'observation du sujet vacciné et les épreuves de laboratoire. C'est la tâche que poursuit depuis des années la *station-pilote du Centre International de l'Enfance* (F. M. Lévy, Ch. Leblois, A. Huet, D. Schwartz, J. P. Pasquier, Raymond Mande). D'autres études voisines ont été poursuivies par l'OMS (Dr J. Holm et enfin par une expérience de plusieurs laboratoires coordonnée par A. Frappier et M. Panisset). On dispose à présent d'un grand nombre de publications intéressantes sur ce sujet important, à propos desquelles nous voudrions ici exposer quelques remarques.

L'élaboration d'une méthode permettant de déterminer l'activité d'échantillons de BCG de sources variées a été le souci commun des chercheurs du Centre International de l'Enfance, cliniciens et expérimentateurs. Sans que des réponses positives aient pu encore être données à toutes les questions posées, une orientation se dégage des constatations déjà faites. Celles-ci concernent principalement le BCG sec. Il ne paraît pas acceptable de se limiter à une seule épreuve quelle qu'elle soit. La méthode que nous proposons cherche à renseigner sur les principales propriétés du vaccin : concentration en bacilles vivants et en bacilles morts, pouvoir allergisant chez l'homme, pouvoir protecteur chez l'animal. Elle tend aussi à permettre, par la confrontation de tous les résultats, d'aborder la question des rapports, jusqu'à présent mal définis, entre ces différents caractères.

(a) Les *comptes de colonies* représentent, de toutes les épreuves, la plus unanimement considérée comme essentielle. Pour y procéder, Ch. Leblois est parti de la technique de Jensen, à laquelle au terme d'investigations minutieuses, il a apporté divers amendements de nature à en augmenter la précision. Mais les dénombrements, quelle que soit la technique suivie, ne permettent pas en réalité de connaître le nombre des germes vivants présents dans l'échantillon étudié. Il en est, en proportion difficile à déterminer, mais sans doute élevée, qui se développent à partir d'un amas de germes plus ou moins important.

La capacité de multiplication des germes *in vitro* est également jugée par la mesure, effectuée par Pasquier, de la fixation par les germes d'isotopes radioactifs incorporés à un milieu liquide : ^{32}P d'abord, à la suite de Ström et de Tubiana, Costil et Mme V. Drouhet, et maintenant ^{14}C dont l'emploi, sous forme d'acétate de sodium, a d'ores et déjà permis des constatations de quelque portée. D'autre part il a semblé intéressant à F. M. Lévy et [illegible] Conge de recourir à des mesures d'exécution simple, photométriques et volumétriques qui permettent de vérifier sommairement, mais avec une approximation

suffisante la régularité des échantillons étudiés quant à la concentration microbienne globale

(b) L'*expérimentation sur l'animal* permet d'aboutir à des résultats qui renseignent sur certaines propriétés capitales de la préparation injectée La cobaye est irremplaçable dans l'appréciation au laboratoire du pouvoir exercé par le BCG de conférer l'allergie tuberculinique et convient bien aussi pour l'observation de la réaction locale (Jensen, Birkhaug Frappier et Marois, Krohn, etc.) Encore faut-il avoir recours à des techniques de mesure aussi quantitatives que possible

Plus importants sans doute comme critères d'activité sont les tests de protection qui permettent de juger directement de l'efficacité du BCG De telles épreuves peuvent être effectuées sur des espèces variées. Nous avons préféré nous adresser à la souris qui se prête particulièrement bien à l'expérimentation en grande série Ces recherches s'inscrivent à la suite de celles de R. J Dubos et C. H Pierce et ont été menées selon la technique des auteurs quelque peu modifiée grâce aux avis de R. J Dubos. Elle consiste à vacciner la souris par une injection de BCG et à l'éprouver par l'injection ultérieure de bacilles virulents. On peut aussi, en se limitant à l'inoculation de vaccin sans la faire suivre d'une injection d'épreuve étudier la multiplication du BCG dans les organes de l'animal

(c) L'*observation clinique chez l'enfant* est indispensable mais l'obligation ou l'on se trouve de toujours employer des doses à la fois efficaces et non excessives, l'impossibilité de disposer à intervalles rapprochés des sujets, même pour un simple examen clinique représentent une servitude dont nul ne songerait à s'affranchir mais qui empêche parfois de pousser les investigations aussi loin qu'on le voudrait. Les renseignements recueillis n'en sont pas moins du plus haut prix, comme touchant directement au point le plus important les résultats de la vaccination par le BCG telle qu'on la pratique. Certes, il est impossible dans l'état actuel des choses de mesurer l'immunité conférée à l'homme et de comparer à cet égard des vaccins de fabrication différente ou plusieurs échantillons de même origine. Les seuls phénomènes qu'il soit aisé d'étudier chez l'enfant sont la réaction locale de la peau l'allergie tuberculinique. L'observation précise et la mesure à dates fixes tant de la réaction locale que du test tuberculinique effectuées dans des groupes suffisamment nombreux, permettent d'enregistrer des résultats variant d'un vaccin à l'autre L'étude de la persistance de l'allergie renseigne peut-être mieux encore sur les différences entre les échantillons utilisés.

La proportion de virages du « Mantoux » à 5 ou 10 unités (PPD) exprime de la manière la plus simple le pouvoir allergisant du BCG employé. Cependant le résultat peut approcher de 100 même avec des produits d'activité assez médiocre Les dimensions moyennes de l'induration du « Mantoux » (à 5 ou 10 unités PPD) constituent un test plus nuancé D'utiles informations sont obtenues aussi en déterminant la proportion des indurations fortes (types I et II selon la terminologie du Bureau de Recherches sur la Tuberculose de l'Organisation Mondiale de la Santé)

D'autres mesures portent sur les dimensions de la lésion locale après injection intradermique Il convient de déterminer

non seulement la taille de l'induration, mais celle de la réaction érythémateuse [C. Fillastre]. Enfin le pourcentage des adénites, simples ou suppurées, consécutives à la vaccination peut également aider à déceler les différences entre vaccins. Tous ces chiffres sont recueillis, en premier lieu, dix semaines environ après la vaccination (premier contrôle). On examine par la suite à nouveau les enfants si possible six mois, un an, deux ans, et parfois trois et même cinq ans après la vaccination. Chaque contrôle porte d'une part sur les tests tuberculiniques, d'autre part sur la cicatrice de la lésion locale.

Une cause importante d'inégalité entre vaccins est représentée par l'origine de la souche. Les « souches-filles » qui dérivent de celle de Calmette ont assurément en commun beaucoup de caractères généraux. Mais elles sont loin de se comporter toutes de façon identique (voir notamment R. J. Dubos et coll., A. Frappier et M. Panisset, H. S. Willis et H. M. Vandiviere). Il en est d'assez « mordantes » et d'autres atténuées à l'extrême. À noter qu'aux « souches-filles » déjà cataloguées, il faut joindre maintenant les souches résistantes à l'isoniazide qui viennent d'entrer en scène.

Ce qui n'apparaît pas clairement à tous, est le rapport entre les caractères des souches-filles que l'on étudie au laboratoire et la valeur clinique des vaccins correspondants. Pourtant il n'est pas douteux qu'à une « virulence résiduelle » trop insignifiante corresponde un pouvoir protecteur diminué. Si on échoue parfois à la démontrer c'est faute d'employer les techniques appropriées.

Le degré d'atténuation de la « souche-fille » utilisée conditionne pour une large part l'activité des vaccins tels qu'on les emploie en clinique et les variations de la souche représentent un des plus grands obstacles à la standardisation du BCG. Soulignons qu'il n'est pas aisé d'apprécier exactement le rôle de ce facteur car les vaccins fabriqués à partir de sous-souches différentes viennent de laboratoires où les techniques de production diffèrent elles aussi.

La comparaison entre vaccins éprouvés à des dates espacées ne fournit donc pas des renseignements aussi précis que la confrontation entre lots étudiés le même jour. Cependant les données que nous avons recueillies en plusieurs années ont montré une régularité suffisante pour qu'il soit possible d'en tirer parti dans leur ensemble, l'exploitation statistique ayant fait apparaître celui-ci comme cohérent — [D. Schwartz et R. Orssaud].

L'analyse de la masse de nos résultats peut donc aider à aborder les questions sans doute les plus délicates que pose le contrôle d'activité du BCG : celles qui ont trait aux rapports des tests entre eux : une des plus grandes *difficultés* rencontrées tenant à la *nécessité de se fonder* à la fois sur les résultats de plusieurs épreuves, exprimant des caractères distincts quoique supposés tous en rapport avec les *propriétés immunisantes* du vaccin.

Les corrélations ne sont pas *très nombreuses* entre les tests cliniques et les tests de laboratoire. Bien entendu, on serait peut-être parvenu à mettre en évidence des corrélations supplémentaires en opérant dans *d'autres conditions* ou à une plus grande échelle. Mais il y a *toutes raisons* de croire que la méthode suivie a

permis de se manifester aux corrélations vraiment étroites

Schématiquement, on peut mettre à part les épreuves *in vitro* et classer les épreuves expérimentales et cliniques, selon leur signification en trois catégories, tests d'allergie tests de virulence tests de protection.

A. *Les comptes de colonies*

(a) *Significations des « nombres d'unités vivantes »* — Ils fournissent une donnée de base indispensable et permettent mieux que les seules mesures pondérales et photométriques, de définir la quantité de vaccin administrée à l'enfant Mais la valeur des chiffres qu'ils fournissent est limitée

On aurait tout-à-fait tort d'admettre que les vaccins les plus riches en unités vivantes sont nécessairement ceux qui protègent le mieux ou qui témoignent du plus grand pouvoir allergisant. Les constatations récentes de Willis et Vandivière sont, comme les nôtres, très démonstratives à cet égard.

(b) *Nécessité du recours aux techniques expérimentales et cliniques* Les comptes d'unités vivantes mis à part il serait tentant de s'appuyer sur d'autres techniques *in vitro* Malheureusement les tests métaboliques et enzymatiques décrits jusqu'à présent ne paraissent pas renseigner beaucoup sur l'efficacité du vaccin. Force est donc de se fonder davantage sur les épreuves expérimentales et cliniques que sur les résultats obtenus *in vitro*

B *Les tests d'allergie*

Ils sont les plus employés. Pratiqués au laboratoire chez le cobaye ils peuvent fournir des renseignements très précis et liés à ceux des tests tuberculiniques effectués chez l'enfant, comme on l'a signalé avant nous comme nous avons pu le vérifier Il y a lieu de mentionner à cet égard les corrélations partielles, à nombre d'unités vivantes constant, que nous avons décelées entre le diamètre du « Mantoux » au premier contrôle chez l'enfant et les résultats obtenus chez le cobaye

Rien n'indique cependant, que le pouvoir immunisant d'un vaccin soit nécessairement parallèle à son pouvoir allergisant.

Il n'y a donc pas à s'étonner que comme nous l'avons constaté il existe des vaccins, doués d'un pouvoir allergisant honorable qui protègent mal la souris. De tels faits incitent en dehors de toute prise de position doctrinale à refuser de voir dans la réponse des animaux ou des enfants aux tests d'allergie après vaccination une garantie suffisante de l'efficacité du vaccin employé

C *Les tests de virulence*

A notre sens il y a lieu d'accorder une place à ces tests qui, pour l'essentiel, traduisent la virulence du BCG Il y aurait lieu d'exiger que les vaccins témoignent chez le cobaye d'un minimum de virulence à en juger par la réaction locale corrigée

D *Les tests de protection*

C'est peut-être dans la difficulté d'arriver à un accord général sur la portée des tests d'allergie et de virulence que réside la meilleure justification du recours aux tests de protection. Le résultat de ceux-ci dépend certes, pour une part des capacités propres de réponse de l'espèce et même de l'individu Mais il traduit aussi les caractères propres du vaccin étudié et

renseigne ainsi sur son pouvoir immunisant.

Faute de pouvoir couramment recourir à des enquêtes cliniques de protection nous tendons à attribuer une valeur particulière aux tests expérimentaux de protection. Il y a assurément quelque arbitraire à juger d'après eux de l'efficacité d'un vaccin chez l'homme mais, dans l'état actuel des choses, on serait bien imprudent de se passer de la caution qu'ils apportent.

Conclusion

L'appréciation des vaccins BCG requiert l'emploi de plusieurs techniques expérimentales auxquelles s'ajoute utilement l'observation de groupes d'enfants vaccinés. La justification d'un tel effort résulte, avant tout, du risque d'efficacité insuffisante couru lorsqu'on vaccine avec un BCG d'activité trop faible. Il est donc proposé de soumettre les fabrications les plus diverses aux mêmes exigences minimales de pouvoir allergisant, de virulence résiduelle et de pouvoir protecteur expérimental. Le dispositif nécessaire même réduit à l'essentiel, demeurant assez lourd il n'est pas aisé de l'employer d'une manière tout-à-fait courante. Mais il pourrait servir par intervalles, au contrôle de chaque type de vaccin. Quant à la régularité de la production elle est appréciée par des comptes d'unités vivantes faites régulièrement.

Bibliographie

(On trouvera la bibliographie complète de ce travail fait avec la collaboration du Docteur F. M. Lévy dans le traité rédigé par cet auteur et ses collaborateurs sous la direction de René Dubos et Robert Debré. Flammarion édit. sous presse.)

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On aurait tout à fait tort d admettre que les vaccins les plus riches en unités vivantes sont nécessairement ceux qui protègent le mieux ou qui témoignent du plus grand pouvoir allergisant. Les constatations récentes de Willis et Vandivière sont comme les nôtres, très démonstratives à cet égard.

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B *Les tests d allergie*

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Il n y a donc pas à s étonner que comme nous l avons constaté il existe des vaccins, doués d un pouvoir allergisant honorable qui protègent mal la souris. De tels faits incitent en dehors de toute prise de position doctrinale à refuser de voir dans la réponse des animaux ou des enfants aux tests d allergie après vaccination une garantie suffisante de l efficacité du vaccin employé

C. *Les tests de virulence*

A notre sens il y a lieu d accorder une place à ces tests qui pour l essentiel traduisent la virulence du BCG Il y aurait lieu d exiger que les vaccins témoignent chez le cobaye d un minimum de virulence à en juger par la réaction locale corrigée

D *Les tests de protection*

C'est peut-être dans la difficulté d arriver à un accord général sur la portée des tests d allergie et de virulence que réside la meilleure justification du recours aux tests de protection Le résultat de ceux ci dépend certes, pour une part, des capacités propres de réponse de l espèce et même de l individu Mais il traduit aussi les caractères propres du vaccin étudié et

Tableau 1 Tableau récapitulatif Les nourrissons sont groupés suivant leur âge au moment de l'E.T

2ème colonne Âge au moment de l'E.T 3ème colonne : Poids à la naissance. 4ème colonne Indication pour l'E.T 5ème et 6ème colonnes pH Valeur avant l'E.T et valeur la plus basse au cours de l'E.T 7ème et 8ème colonnes K valeur avant l'E.T et valeur la plus haute au cours de l'E.T

Cas No.	Âge (heures)	Poids de naissance (g)	Diagnostic	pH Initial	pH Le plus bas	K (mEq/L) Initial	K (mEq/L) Le plus haut
1	1	2'840	Incompatibilité anti-D	7,36	7,20	4,9	4,4
2	2	2'[illegible]	Incompatibilité anti-D	7,33	7,22	4,8	5,6
3	5	2'770	Incompatibilité anti-D	7,33	7,22	4,8	5,6
4	7	3'200	Incompatibilité anti-D	7,33	7,27	5,1	5,1
5	10	3'050	Incompatibilité anti-D	7,33	7,19	4,8	5,3
6	10	3'900	Incompatibilité anti-D	7,34	7,20	4,4	5,7
7	10	3'450	Incompatibilité anti-D	7,40	7,30	3,7	4,1
8	18	3'[illegible]	Incompatibilité anti-D	7,30	7,33	3,5	10,3
9	22	3'250	Incompatibilité Lewis + A–O	7,35	7,31	3,5	3,5
10	26	4'400	Incompatibilité A–O	7,37	7,37	3,5	4,1
11	36	3'780	Hyperbilirubinémie	7,36	7,29	4,5	4,5
12	37	3'410	Incompatibilité A–O	7,36	7,33	4,2	4,2
13	38	3'100	Incompatibilité A–O	7,31	7,33	3,2	[illegible]
14	43	3'210	Incompatibilité A–O	7,38	7,33	3,5	3,5
15	48	3'400	Incompatibilité A–O	7,41	7,29	3,8	3,8
16	72	3'620	Incompatibilité A–O	7,36	7,26	3,7	3,8
17	85	3'200	Hyperbilirubinémie	7,29	7,29	1,9	4,5
18	[illegible]	3'820	Hyperbilirubinémie	7,42	7,35	4,4	4,8
19	104	3'310	Incompatibilité A–O	7,35	7,24	—	—
20	108	3'060	Hyperbilirubinémie	7,27	7,30	4,1	4,9
21	120	3'450	Hyperbilirubinémie	7,42	7,46	3,9	4,6
22	125	4'200	Hyperbilirubinémie	7,41	7,33	4,1	4,1
23	136	3'050	Incompatibilité A–O	7,34	7,33	4,2	4,9
24	152	2'840	Incompatibilité AB–B	7,46	7,41	3,6	3,6
25	168	3'[illegible]	Hyperbilirubinémie	7,41	7,30	4,5	4,6

bleau 2, où nous avons indiqué la moyenne des dosages effectués et, dans la parenthèse, les valeurs extrêmes. Pour le pH ce sont les valeurs maximales et minimales qui sont notées. Les différences sont particulièrement frappantes pour le pH, le potassium et le chlore; elles sont insignifiantes pour le calcium, le sodium et l'hémoglobine.

Le pH Théoriquement, la transfusion de sang citraté, dont le pH varie entre 6,4 et 6,7 (voir tableau 2) va causer une acidose métabolique par apport supplémentaire de ions H, acidose que les tampons de l'organisme et les régulations rénales et pulmonaires vont vraisemblablement tenter de compenser. Dans un deuxième temps, le citrate lui même sera métabolisé et transformé en bicarbonate, produisant ainsi une alcalose métabolique. Ces deux *phénomènes seront* d'autant plus nettement distincts l'un de l'autre que l'E.T aura été effectuée plus rapidement. Les différentes mesures effectuées sont résumées dans la figure 1, chaque ligne représentant les valeurs individuelles d'un seul sujet. Comme on pouvait le prévoir le pH baisse chez la plupart des nourrissons dès le début de l'E.T. Il se normalise spontanément par la suite et

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Acides-bases et électrolytes au cours de l'exsanguino-transfusion à l'aide de sang citraté

*Communication préliminaire**

par G DUC et G DE MURALT

Les critiques formulées à l'égard de l'emploi de sang citraté pour l'exsanguino-transfusion (E. T) [8 9 14 15] nous ont incités à contrôler les variations de l'équilibre acide base et des électrolytes au cours de 25 échanges effectués chez des nouveaux nés hyperbilirubinémiques.

Matériel et méthode

5 nouveaux nés âgés de 1–189 heures ont fait l'objet de cette étude. Leur poids, leur âge respectif le diagnostic étiologique de l'hyperbilirubinémie sont indiqués dans le tableau 1 Aucun ne présentait de symptômes cliniques d'une affection respiratoire ou cardiaque

Les dosages suivants ont été effectués : pH (microméthode d'Astrup) sodium, potassium, chlore (méthode titrimétrique) calcium (méthode photométrique d'Eppendorf) hémoglobine (méthode à la cyanmethémoglobine) lactate et pyruvate (méthodes à la déhydrogénase lactique [11])

La pCO_2, le déficit ou l'excès de base ont été calculés à partir des valeurs du pH à l'aide du nomogramme de Siggaard Andersen [13]

Ces diverses mesures ont été effectuées :

(a) dans les flacons de sang utilisés après prélèvement du liquide citraté surnageant les érythrocytes sédimentés;

(b) chez tous les nourrissons avant l'E.T puis tous les 200 ml de sang transfusé et enfin 12 à 16 heures après la fin de l'E.T

Le pH a été déterminé dans le sang capillaire prélevé au talon après avoir trempé le pied pendant 10 minutes dans un bain d'eau à 40 degrés. Aucun des nourrissons n'ayant présenté de cyanose les corrections pour la désaturation n'ont pas été nécessaires.

Les dosages de sodium, potassium, chlore, calcium lactate et pyruvate ont été effectués dans le sang veineux prélevé par le cathéter ombilical, après avoir d'abord aspiré et jeté 10 ml de sang de façon à éviter toute contamination avec le mélange injecté

Le sang utilisé pour l'E T avait été prélevé au centre de Transfusion de la Croix Rouge Suisse à Berne chez des adultes sains. La solution anticoagulante ACD utilisée contient 0 47 % d'acide citrique 1 6 de citrate de sodium 2,5% de dextrose son pH est de 5 2.

100 ml d'ACD sont mélangés à 400 ml de sang

Résultats

La transfusion de sang citraté à un nouveau né va entraîner des modifications ioniques que les différences de composition entre le sang des donneurs et celui des nourrissons permettent de prédire Ces différences ont été résumées dans le ta

* L'article in extenso paraîtra plus tard.

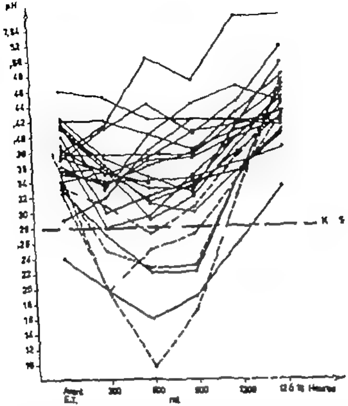

Fig. 1. Variations du pH au cours de l'E.T. Chaque ligne représente les valeurs individuelles d'un seul sujet. Tous les pH inférieurs à 7,28 (ligne horizontale) ont été mesurés chez des nouveau-nés âgés de moins de 12 heures au moment de l'E.T. Tous ces sujets ont présenté parallèlement à la baisse du pH, une élévation du potassium à des valeurs supérieures à 5 mEq/L. (K > 5, voir fig. 4).

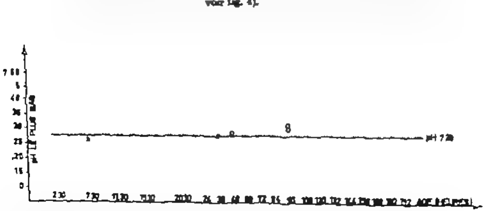

Fig. 2. Chaque cercle ou croix représente le pH le plus bas mesuré chez un sujet par rapport à son âge au moment de l'E.T. Tous les sujets, sauf un seul, âgés de moins de 12 heures au moment de l'E.T. ont présenté des pH inférieurs à 7,28.

TABLEAU 2. *Valeurs extrêmes du pH et moyennes des taux de potassium chlore, sodium calcium hémoglobine.*

Déterminations dans les 9 flacons de sang citraté (après prélèvement du liquide surnageant les érythrocytes sédimentés) et chez les nourrissons avant l'Ex.T Valeurs extrêmes dans la parenthèse

	Donneur (Citrat)	Nourrisson avant E.T
pH	6,4–6,7	7 24– 46
K mEq/L	7,3 (3 1–16,0)	4,3 (3, –5,1)
Cl mEq/L	63,3 (33–73)	117 (101–1*0)
Na mEq/L	14g (139–160)	143 (134–153)
Ca mgr %	8,0 (6,4–10,0)	9,0 (4,6–1_,8)
Hb gr %	16,4 (9 3–19,9)	14 8 (11 7–18,9)

atteint dans certains cas, des valeurs nettement alcalines comme on s y attendait également

L étude des variations simultanées du déficit de base et de la pCO_2 a montré que tous ces sujets présentaient dans un premier temps une acidose métabolique non compensée transformée ensuite en alcalose métabolique également non-compensée puisque la pCO_2 restait constante malgré la baisse importante du pH Ce fait a également été observé par Calladine et al [2] Ces diverses variations sont vraisemblablement sans importance biologique pour la plupart des sujets, car elles ne sont que de courte durée se normalisent spontanément et n atteignent pas des valeurs extrêmes. Pour six d entre eux cependant, c est l acidose qui est particulièrement frappante puisque les pH mesurés sont inférieurs à 7,23 et atteignent 7 10 même

L analyse détaillée des caractéristiques respectives de ces sujets a montré qu ils ne se distinguaient des autres ni par leur poids, ni par leur degré de maturation, ni par la rapidité avec laquelle l exsanguino transfusion avait été effectuée ni par le pH du sang des bouteilles utilisées. Un seul facteur commun à tous a pu etre retenu ces nourrissons étaient âgés de moins de 12 heures au moment de l échange.

Ce fait est illustré plus clairement dans la figure 2 où nous avons représenté la valeur la plus basse des pH mesurés chez un sujet par rapport à son âge au moment de l E T

Comme on peut le constater tous les nourrissons âgés de moins de 12 heures, à l exception d un seul ont présenté des pH inférieurs à 7,28 alors que chez les autres transfusés pourtant dans les mêmes conditions, le pH est resté supérieur à 7,28.

Ainsi il apparaît que l organisme dans les premières heures de la vie est moins à même de lutter contre l acidose métabolique imposée par la transfusion de sang citraté. On peut supposer que l immaturité des fonctions hépatiques (retard dans la métabolisation du citrate) et rénales (réponse tubulaire insuffisante à l acidification) sont à l origine de ce fait

Lactate et pyruvate

Le taux de lactate et de pyruvate varie entre 0,2 mMol/L et 5 mMol/L. Ces valeurs sont légèrement supérieures aux données de la littérature [6, 13]. Les sujets les plus jeunes présentaient les valeurs les plus hautes comme l ont déjà relevé d autres auteurs [13 16]. Durant l E.T le taux de lactate reste pratiquement constant Aucune corrélation n a pu être mise en

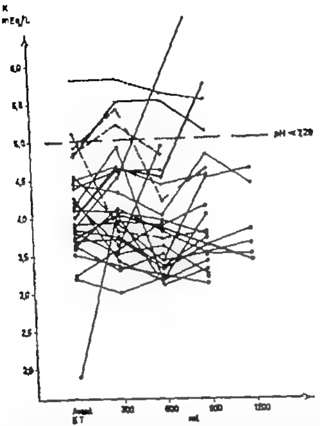

Fig. 4. Variations du K au cours de l'E.T. Chaque ligne représente les valeurs individuelles d'un seul sujet. Le sujet qui présente un K à 10,2 mEq/L à la fin de l'échange a reçu un flacon de sang contenant 16 mEq/L. Tous les autres sujets qui ont présenté de valeurs de K supérieures à 5 mEq/L avaient des pH < à 7,20 et étaient âgés de moins de 12 heures au moment de l'E.T (voir fig. 1).

Qu'en est-il en réalité?

Les variations du taux de potassium durant l'E.T. sont résumées dans la fig. 4. Pour la plupart des sujets, les fluctuations constatées sont vraisemblablement sans importance biologique, puisqu'elles restent dans les limites des normes. Pour six d'entre eux cependant, les valeurs sont supérieures à 5,0 mEq/L et s'élèvent même à 10,2 mEq/L dans un cas. Fait digne d'intérêt, cinq de ces sujets sont âgés de moins de 12 heures et ont présenté les pH les plus bas (fig. 2). Le nourrisson qui a présenté un taux de potassium à 10,2 mEq/L à la fin de l'échange était âgé de 18 heures, mais avait reçu à notre insu un flacon de sang contenant 16,0 mEq/L de potassium. Il n'a présenté aucun symptôme clinique. Il est à noter qu'un autre sujet, qui reçut un flacon de sang contenant 11,2 mEq/L n'a pas présenté d'hyperpotassémie.

Ainsi, tout comme pour le pH, l'hyperpotassémie constatée semble être en rap-

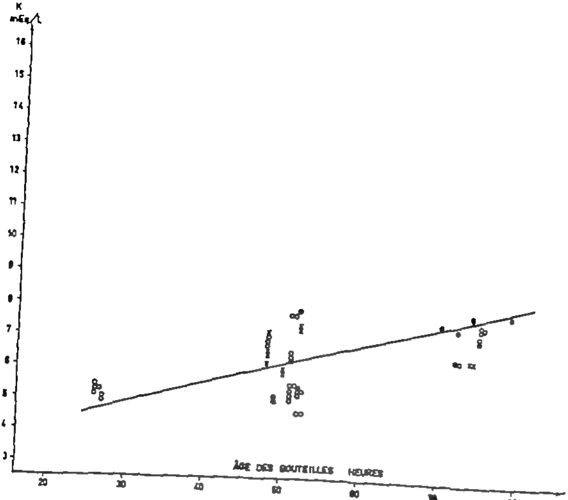

Fig. 3. K plasmatique dans l sang citraté « donneur » par rapport au temps écoulé après la prise de sang et son emploi pour l E.T

évidence entre la lactacidémie et les variations du pH

Le taux de pyruvate varie avant l E T entre 0,02 mMol/L et 0,20 mMol/L. Les variations du pyruvate sont sans rapport avec le pH

La dispersion des valeurs est en partie due aux difficultés de la méthode utilisée (déhydrogénase lactique : Richterich [11]) Ces résultats démontrent cependant que l acidose présentée par les nourrissons transfusés dans les premières 12 heures est sans rapport avec des variations du quotient lactate/pyruvate

Le potassium

Le taux de potassium plasmatique du sang citraté augmente progressivement dans les heures qui suivent la prise Ce fait a été relevé par d autres auteurs [4 7 10], nous l avons également vérifié (fig 3) Tous les flacons de sang utilisé plus de 70 heures après la prise contenaient plus de 6,4 mEq/L de potassium dans deux d entre eux ces valeurs s élevaient même à 11,2 mEq/L et 16,0 mEq/L.

Il est à prévoir que la transfusion d un tel sang à un nouveau né pourra entraîner une élévation de la potassémie

progressive durant tout l échange. Tout se passe comme si aucun mécanisme de contre-régulation ne tentait à s opposer à l'hypochlorémie que l'on impose à l orga nisme.

Ces perturbations sont sans rapport avec les variations du pH, du taux de potassium ou de sodium elles ne sont pas plus importantes chez les sujets transfusés dans les premières 12 heures.

Le sodium

Le taux de sodium dans les flacons de sang tilisé étant pratiquement le même que chez les nourrissons, on pouvait d avance prévoir qu il varierait peu au cours de l'E.T Ce fait a été vérifié.

Le calcium

Les variations du taux de calcium sont minimes u cours de l'E.T Tous nos sujets avaient reçu, comme il est coutume de le faire 1 ml de gluconate de calcium à 10 %. tous les 100 ml de sang transfusé. Ces résultats démontrent seulement que le taux de calcium total ne varie pas u cours de nos E.T

Il serait cependant erroné de conclure que le taux de calcium biologiquement actif (calcium ionisé) a été toujours suffi sant a cours de l'échange Notons cepen dant qu aucun sujet n a présenté de symptômes de tétanie.

Conclusions

L emploi de sang citraté pour l exsan guino-transfusion des nourrissons hyper bilirubinémiques, exempts d affections pulmonaires ou cardiaques, provoque une acidose métabolique non compensée avec hyperpotassémie chez les sujets âgés de moins de L heures. L acidose métabolique fait place à une alcalose métabolique non compensée dans les 1 à 16 heures qui suivent l échange

D autre part chez tous les sujets le taux de chlore baisse progressivement au cours de l échange alors que le sodium et le calcium restent inchangés. Ces différentes variations ne s accompagnant d aucun symptôme clinique et se normalisant spon tanément, il nous parait injustifié d aban donner systématiquement l emploi du sang citraté pour recourir au sang héparmé

Les précautions suivantes sont à con seiller

1 Le liquide surnageant les érythrocytes sédimentés sera prélevé avant l échange de façon à diminuer autant que possible l apport d'ions H.
2. Le sang des donneurs ne doit être utilisé que moins de 48 heures après la prise de sang, de façon à éviter l'hyperpotassémie.
3. L exsanguino-transfusion doit être f fectuée particulièrement lentement (moins de 5 ml/kg/min) chez les sujets âgés de moins de 12 heures, chez lesquels d autre part il est à conseiller de déterminer au cours de l échange, le pH.
4. Toute acidose métabolique durable sera corrigée à l aide de bicarbonate par voie intraveineuse. La quantité de bicarbonate à injecter dépendra du pH

Des études complémentaires sont en cours pour déterminer si l emploi systématique de bicarbonate ou de Tris doit être recommandé.

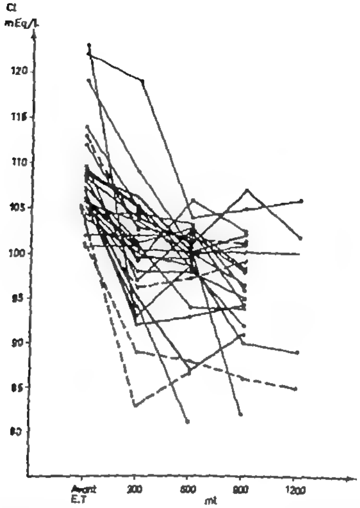

Fig 5. Variations du Cl au cours de l'E.T Chaque ligne représente les valeurs individuelles d un seul sujet. La chlorémie baisse progressivement au cours d l E.T Les sujets âgés de moins de 12 heures au moment de l'E.T (lignes épaisses ou tratillées) ne se distinguent pas des autres.

port étroit avec l âge du nourrisson au moment de l E.T , puisque les sujets plus âgés, qui avaient pourtant été transfusés avec des flacons de sang contenant des taux de potassium analogues n ont pas présenté d hyperpotassémie

L augmentation du potassium plasmatique chez les sujets âgés de moins de 12 heures est vraisemblablement en rapport avec l acidose métabolique qu ils ont présentée, la baisse du pH provoquant une fuite du potassium intra-cellulaire dans le plasma. Ce phénomène a été démontré in vitro par Fenn et Cobb [3], et in vivo chez l animal par Keating *et al* [6], chez l'homme par Burnell *et al.* [1]

Le Chlore

L'hypochlorémie constatée dans tous les flacons de sang (tableau 2) va provoquer vraisemblablement un abaissement du taux de chlore chez les nourrissons Ce fait a été constaté dans tous les cas (fig 5) La baisse du taux de chlore est d autant plus importante que la chlorémie était plus basse au départ, cette baisse est

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From the Children's Hospital and the University Sheffield, England

Evidence from Bone Growth that Most of the Infants Dying in the Neonatal Period had been Ill Before Birth

by JOHN L. EMERY

The subject that I have chosen for inclusion in this volume in honour of Professor Constantin Choremis arises from our very first conversation. When, nearly ten years ago, my old colleague and friend Spiros Doxiadis first introduced me to Constantin Choremis, he asked me to speak to his unit. I did so on some problems of bone growth in the foetus.

It was in private conversation following this that I began to realise the wide and philosophical under-current that lay behind Choremis's remarks and it was then that I first began to appreciate the hidden depths of this unusual man, a man to whom the growth of the trees in his garden, the growth of bones, and the growth of ideas were as one thought.

Greece has long been the classic site of the study both of philosophy and of archeology and the investigations discussed here are essentially the employment of an archeological concept, an attempt to read into the pattern of structure of the newborn bones, the previous history of the child. We in Sheffield have also been particularly fortunate in being associated in this work by a paediatrician pupil of the Athens school of Medicine, Pitsa Kalpaktsoglou.

The period after the 1914-18 European war was the time when the pathology of rickets, scurvy and the great deficiency diseases of childhood was largely worked out by Follis and Park in the United States [1, 2, 3, 4]. There was also the fascinating correlation of the radiological findings in bone of lines of growth arrest described by Harris [5]. This work is summarised in a magnificent way by Park in 1964 in his Goldberg Lecture [4]. He shows how postnatal general and nutritional diseases leave lasting effects on the structure of the bones of the child. That work concerned childhood and those who worked on the osseochondral junctions of children dying in the newborn period, simply remarked that these, too, showed the changes of rickets.

Approximately fifteen years ago we first started using the results of Park's study as a means of assessing the previous health of children who had been found unexpectedly dead (the so-called 'cot deaths') and, having found this to be extremely useful [6], went on to attempt to apply the same principals to perinatal deaths.

Most clinical work on bone has been done on the lower end of the femur and

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TABLE 1 *The major criteria for the assessment of the costochondral junction.*

	Criteria for grouping the ribs		
	Normal	Simple growth retardation	Bizarre growth
Junctional line	Distinct	Very definite	Indistinct
Cartilage columns	Cells in straight, single or double columns—simple/compound, straight	*Cells in straight single or double columns—simple/compound, straight*	*Irregular compound, complex with many cells in irregular clusters*
Thickness of Zone I, the layer of swollen cartilage cells in columns	0.03–0.04 mm	Diminished	Increased or normal
Thickness of Zone II, the layer of cartilage cells between the resting cells and the swollen ones above	0.06–0.09 mm	Normal or diminished	Very variable
Bridging of matrix across the ends of the cartilage cells	Minimal	Present	Present
Bandings of matrix left behind in the bone	Absent	Present	Present
Matrix pools, masses of cartilage matrix reaching the bone	Few	Variable	Many irregular

reached and each column of cells leaves behind at its side, a thin film of matrix (Fig. 1).

If for any reason, there is a diminution in the rate of growth, the 'firing' rate of the cells diminishes and two things become rapidly obvious. First, there is a thickening and irregularity of the strands between the cartilage columns and second if at any *time* the *actual discharge* of cells ceases, then a thin cap of matrix occurs between the terminal cartilage cell and the marrow cavity. If this process continues for any length of time a cross-banding of matrix occurs (Fig. 1*b*) often over-capping several cartilage cell columns. At the same time the marrow cavity continues to absorb the trabeculae so that there is bridging of trabeculae over groups of cartilage columns.

When the rate of growth is intermittent, the cartilage cells proliferate behind these bands *and bridges and the latter are left* behind within the bone as a series of tide-marks which correspond at a microscopic level to the calcified cross-striation in bone known clinically as Harris's lines. These cross bands cannot be shown on an x ray plate both because of their size and because they are not usually deeply calcified. In practice, this type of lesion can very frequently be found.

When there has been disturbance of growth over a continuous period with incomplete cessation of growth, the whole costochondral junction loses its general regular form, the bands of matrix that are left behind in the bone are similarly irregular and the cartilage columns lose their direct longitudinal orientation. This is a picture which we describe as bizarre [7] (Fig. 1*c*). It has some superficial resem-

Fig 1 Photographs of costochondral junctions from three children, all perinatal deaths. (a) A normal junction Note the long rows of cartilage cells leading off directly into the bone with long thin strands of trabeculae matrix. (b) A junction showing a period of growth retardation. Note the great increase in the amount of cartilage matrix and the building up of this matrix between the cartilage cells and the bone marrow (c) A junction showing a bizarre picture. The general junction line is not obvious and there are irregular masses of matrix. The marrow blood vessels are also penetrating in an irregular manner and the cartilage cells occur in large irregular nests.

the head of the radius, largely because these bones are most easily available for x ray studies, but, for doing microscopic studies, the rib is much better as it is probably the most rapidly growing long bone and it grows in a linear fashion throughout almost the whole of intra uterine life The more rapid the basic growth rate of a tissue the more obvious and early are the effects of growth arrest

The costochondral junction normally appears as a series of columns of cartilage cells between strands of cartilaginous matrix and these strands continue on into the bony trabeculae. This has a rather rigid and static appearance

The costochondral junction, however is an extremely active structure. A fully distended cartilage cell is about 14 μ thick. When the size of the cartilage cells is taken into consideration together with the increasing length of the bone (0 43 mm or 430 μ a day) we find that at least the length of a whole column of the ballooned cartilage cells must be replaced every day If we were able to look at the living costochondral junction the actual blowing up of the small cartilage cells into the large, ballooned cells is so rapid that it could almost be seen occurring The costochondral junction is thus not a static structure at all, but much more like a series of small rockets or a sort of slow firing multi barrelled jet, the cartilage cells distend and burst into the cartilage cavity so that the cartilage recedes from the shaft leaving a slip-stream of matrix behind.

In the fixed section of the normal costochondral junction, the marrow ends of these rockets (columns of cartilage cells) are open. There is a progressive increase in size of the cells as the marrow cavity is

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Cartilage columns	Cells in straight, single or double columns—simple/compound, straight	Cells in straight single or double columns—simple/compound, straight	Irregular compound, complex with many cells in irregular clusters
Thickness of Zone I, the layer of swollen cartilage cells in columns	0.03–0.04 mm	Diminished	Increased or normal
Thickness of Zone II, the layer of cartilage cells between the resting cells and the swollen ones above	0.08–0.09 mm	Normal or diminished	Very variable
Bridging of matrix across the ends of the cartilage cells	Minimal	Present	Present
Bandings of matrix left behind in the bone	Absent	Present	Present
Matrix pools, masses of cartilage matrix reaching the bone	Few	Variable	Many irregular

reached and each column of cells leaves behind at its side, a thin film of matrix (Fig. 1a).

If for any reason, there is a diminution in the rate of growth, the "firing" rate of the cells diminishes and two things become rapidly obvious. First, there is a thickening and irregularity of the strands between the cartilage columns and second if at any time the actual discharge of cells ceases, then a thin cap of matrix occurs between the terminal cartilage cell and the marrow cavity. If this process continues for any length of time a cross-banding of matrix occurs (Fig. 1b), often over-capping several cartilage cell columns. At the same time the marrow cavity continues to absorb the trabeculae so that there is bridging of trabeculae over groups of cartilage columns.

When the rate of growth is intermittent, the cartilage cells proliferate behind these bands and bridges and the latter are left behind within the bone as a series of tide-marks which correspond at a microscopic level to the calcified cross-striation in bone known clinically as Harris's lines. These cross bands cannot be shown on an x ray plate both because of their size and because they are not usually deeply calcified. In practice, this type of lesion can very frequently be found.

When there has been disturbance of growth over a continuous period with incomplete cessation of growth, the whole costochondral junction loses its general regular form the bands of matrix that are left behind in the bone are similarly irregular and the cartilage columns lose their direct longitudinal orientation. This is a picture which we describe as bizarre (7) (Fig. 1c). It has some superficial resem-

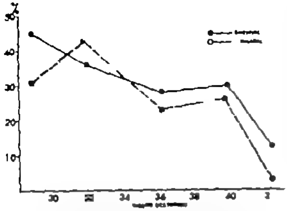

Fig. — The perinatal child deaths have here been grouped on gestational age at birth, based on the last menstrual period. The proportion of rib ends that appear to be within normal limits are recorded for the Sheffield series and for those available from the rest of the United Kingdom through the Perinatal Mortality Survey

blance to the changes seen in rickets during infancy and it is this picture which undoubtedly led the early workers to consider that the normal costochondral junction of the newborn showed the changes of rickets. The criteria for assessment of the ribs are shown in Table I. These changes in the growing ribs seen in neonates correspond very closely with those described in older children by other workers [8].

Material Studied

We have done histological examinations on the ribs of every child coming to necropsy for the past fifteen years and our observations are thus based upon examination of the costochondral junction of the ribs of over 4,000 children, over 2,000 of which died in the perinatal period. The details of handling the ribs and assessment and measurement are described elsewhere [7].

The assessment of normal structure is one of the most difficult in pathology of the newborn period. Since we have very frequently seen obvious signs of intrauterine disease, such as fatty liver, in children who have apparently died from trauma to the brain during delivery, we have been extremely strict in our criteria for assessing normals. The only ribs that we have accepted as being normal have come either from children who have died immediately *in utero* as a result of a pregnant woman being involved in a road accident, or from children dying during labour as a result of vasa previa. We have not accepted placenta previa.

Results of Recent Survey of 1 064 Perinatal Deaths

Kalpaktsoglou and I recently made a definitive study of ribs from a series of 1 064 perinatal deaths. The cases came from two groups of children, 684 consecutive cases from the files of the Children's Hospital in Sheffield and 380 coming from children who had come to necropsy during the recent Mortality Survey [9] carried out in England in 1961 and in which the pathologists had kindly sent me the ribs of all their cases dying during the selected month. We had, thus, our own fairly large series and a smaller, almost random group from the whole of the rest of the United Kingdom.

Of the total of 1 064 ribs, 332 only could be considered as within the range of normal and 732 showed what we considered to be definite changes indicating that the child had been ill and not growing for at least a week prior to the onset of labour.

The full details of the cases and results are presented elsewhere [ ]. The results were analysed in a variety of ways including gestation age, body length and history.

When we studied our findings from the point of view of the proportion of deaths at different gestational age showing no significant rib growth disturbance, we found that the instances of lesion in the Sheffield series coincided almost exactly with those obtained from ribs of children

dying elsewhere (Fig 2). The trend of both these series is quite distinct and statistically valid. The gestational age at which the highest proportion showed no evidence of intrauterine disease was less than 32 weeks when the proportion was around 40%. As the deaths occurred at later gestational ages, the proportion of children with normal ribs diminished progressively so that around full term, the proportion was only bout 25% and this figure reached 6% only in one group of children dying after prolonged gestation (42+ weeks)

If these assessments are correct, the implications appear to be that in the perinatal period, the great majority of deaths occur in infants that have been ill long before the onset of labour and that this applies mostly to the children born around term. This does not mean necessarily that birth trauma or other stresses of labour had no part in these children's deaths, for in children already ill, the "normal trauma of birth would be of greatly increased importance. It would seem to imply however that if we are to further diminish perinatal mortality we must look with greater concentration at the foetus during later pregnancy for evidence of diminution in growth rate or of some chemical indication of intrauterine athrepsia in order to shield these infants during labour or induce labour while the child is fit enough to stand its stress.

Summary

A survey of the pattern of growth, as revealed by the structure of the costochondral junction, suggests that the great majority of infants dying in the neonatal period had intrauterine disease antedating labour This involves approximately 90% of premature birth deaths and around 75% of perinatal deaths at term.

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The Differentiation and Maturation of Specific Immune Mechanisms

by DAVID GITLIN

The capacity of the mature individual to repel the hostile incursions of infectious organisms is dependent upon the complex interaction of a number of different factors, each of which to be entirely effective as part of the defense system must operate for the most part in unison with the others. The factors involved may be specific in that they have a selective action against only a specific agent or against a small group of structurally similar agents, or they may be nonspecific in that they are directed against relatively large groups of different organisms. The specific factors of immunity are of course the antibodies, since an antibody may be defined as any substance which is synthesized by the body in response to antigenic stimulation and which will react specifically or almost exclusively with that antigen. Nonspecific factors include such obvious physical barriers as the skin and mucous membranes proteins such as lysozyme and interferon, and cell populations such as the granulocytes and the reticuloendothelial system Some of the nonspecific factors have limited effectiveness independently of the specific factors, but most perform more efficiently when specific antibodies are also present, and some are entirely dependent upon antibodies for effective action. On the other hand, antibodies alone have little or no direct lethal action against the bacteria and some viruses at least and for bactericidal activity specific antibodies require the coordinated intercession of such nonspecific factors as the granulocytes, the reticuloendothelial system or complement It is clear then that a deficiency of but a single factor in the immune system may result in a partial or complete failure of the defense Since most of these factors, both specific and nonspecific differentiate at different stages of fetal and neonatal development and mature at different rates one from the other one or more immune factors will be deficient or absent at any given time during early development Thus, in the period between early intrauterine life and early childhood, the ability of the individual to resist infection changes dramatically It is the purpose of this discussion to describe the differentiation and maturation of specific immunological factors and to relate these factors to immunity against infection.

It is almost unnecessary to state that all antibodies are of intracellular origin. Some cells synthesize antibodies and release them into the plasma as free proteins

known as immunoglobulins; still other cells synthesize antibodies which remain, for the most part at least, as an integral part of the cell. The latter type antibodies, often referred to as cellular antibodies, are synthesized primarily in small lymphocytes; the immunoglobulins are synthesized by plasma cells and related lymphocytoid cells. A deficiency in antibody synthesis, therefore, theoretically may result either from a deficiency or absence of those cells responsible for antibody synthesis, or from a deficiency or suppression of any of the antibody synthesizing steps from DNA coding of messenger RNA to final antibody release either from the cell or from the ribosome.

The Immunoglobulins

Structure. The immunoglobulins of plasma migrate electrophoretically as γ_1 and/or γ_2-globulins; for the present at least, they have been classified into five major classes or groups. Each of these immunoglobulin groups has, over the years, acquired a number of different names as each investigator categorized the newly discovered proteins according to different systems of protein classification. To obtain some degree of uniformity in nomenclature still another system of classification was recently adopted by a conclave of workers in this field and this system is sometimes referred to as the WHO nomenclature [1]. Although all of the previously recorded names of each of the immunoglobulins admittedly have equal validity the latter nomenclature will be used here and the reader is referred to Table 1 for the older and perhaps more familiar designations.

Three immunoglobulin classes, γG (IgG) γA (IgA), and γM (IgM) together account for over 99% of all the plasma γ-globulins and thus represent the bulk of the total plasma antibodies (Table 1). The remaining relatively small amount of immunoglobulins includes γD (IgD) [2] and a group of γ-globulins of relatively low molecular weight [3, 4]. The γG immunoglobulins are primarily γ_2-globulins on electrophoresis, while γA, γM and γD are γ_1 globulins. The low molecular weight γ-globulins represent both γ_1 and γ_2-globulins. Each immunoglobulin molecule with the exception of the low molecular weight γ-globulins consists of equal numbers of two quite different polypeptide chains, the light chains and the heavy chains; the low molecular weight plasma γ-globulins are composed only of structures immunologically related to the light chains and lack heavy chains. The light chains in each immunoglobulin class are similar to those found in each of the other classes [5–7] and can be differentiated into two types which differ markedly in peptide structure: the κ-chains and the λ-chains [8–10]. On the other hand, the heavy chain in each immunoglobulin class is characteristic of that class and differs from the heavy chains of each of the other immunoglobulin classes: the heavy chains of γG have been designated γ-chains while those of γA, γM and γD are termed α-chains, μ-chains and δ-chains, respectively [1]. The light and heavy chains are held together in the molecule by means of disulfide bonds, the heavy chains imparting the structures responsible for much of the antibody activity although maximum antibody activity requires light chains as well as heavy chains [11–13]. A given

TABLE 1 *Plasma immunoglobulins Metabolic rates*

WHO nomenclature	Earlier names	Molecular weight	Plasma concentration mg/100 ml	Plasma concentration µmoles/100 ml	Half life (days)	Synthesis mg/kg/day	Synthesis µmoles/kg/day
γG or IgG	γ, γ_2, γSS, 6.6Sγ, 7S γ	±155 000	1 000 (600–1800)	6	25	28	0.17
γA or IgA	β_2A, γ_1A, 7S–14S γ	±155,000 (400,000)	90 (30–100)	0.5	7	7–11	0.04–0.07
γM or IgM	γ_1 macroglobulin, β_2M, γ_1M, 19S γ	±800,000	80 (50–100)	0.1	10	5–8	0.006–0.01
γD or IgD	γ_1D	±155,000	3 (0.3–40)	0.2	—	—	—
$\gamma_{K,L}$	Low molecular weight	±15,000	0.1	0.007	0.4	0.18	0.01

γ-globulin molecule may contain either κ chains or λ-chains, but not both; those molecules which have κ chains are said to be type K molecules and those with λ-chains are type L molecules. Both type K and type L molecules are usually found in the same person.

To recapitulate, the γ-globulins are at present divided into five different groups on the basis of differences in heavy chain composition and each of these classes can be further divided into type K or type L molecules depending upon the light chains in the molecule. The molecular structure of γG therefore may be written as $\kappa_2\gamma_2$ or $\lambda_2\gamma_2$. γG has a molecular weight of approximately 155 000 and the individual isolated light and heavy chain units have weights of 20 000 and 55 000 respectively [11–14]. Similarly γA, γM and γD have the following structures, respectively: $(\kappa_2\alpha_2)_n$ or $(\lambda_2\alpha_2)_n$; $(\kappa_2\mu_2)_n$ or $(\lambda_2\mu_2)_n$; and $\kappa_2\delta_2$ or $\lambda_2\delta_2$. For most of the γA in plasma $n = 1$ and the molecular weight is similar to that of γG, but some of the molecules of γA have higher molecular weights and for these n may be 2, 3 or 4. The molecular weight of γM is approximately 800 000 to 1 000 000 so that n in the structural formula is either 5 or 6.

But the heterogeneity in γ globulin structure is far more complex than is indicated by their separation in five major divisions or even ten subclasses. And even the less obvious structural modifications are more than simply of academic interest, since as will be shown, these variations relate to differences in function and metabolism and, consequently, have clinical significance. The κ chains can be divided into subgroups on the basis of structural differences designated as Inv groups [15, 16] and the heavy chains may differ in structural components called the Gm groups [17, 18]. There are at least two different Inv groups and at least seven or eight different Gm groups known, all of which are genetically determined and modify the structure of the γ globulin molecule. A person homozygous for a given Gm allele can nevertheless synthesize some γ globulin molecules lacking that

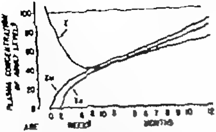

Fig. 1 The relative changes in the plasma concentrations of γG, γA and γM with age. The abscissa changes coordinates to months after 10 weeks of age.

specific Gm structure to add to the complexity. There are at least four genetically determined variations in the γ-chain structure of γG which have been identified in addition to those already mentioned, two of them being related to specific Gm groups [19]. And there is evidence to indicate that a specific antibody activity is related to the primary structure of the γ-globulin molecule so that each specific γ-globulin antibody differs in fundamental structure from all other γ-globulin molecules having a different antibody specificity [20–22].

The γ-globulins found in plasma are not the only immunoglobulins present in the body fluids. To the contrary normal urine, saliva and colostrum at least, and probably the bronchial secretions as well, contain γ-globulins *not found in plasma* as well as some of those present in plasma. At least four immunoglobulins which are similar in structure to each other have an average molecular weight of 12 000 and thermoprecipitation properties like those of Bence Jones proteins are found in normal urine, but in small amounts [4 23–26]. Unlike plasma, the immunoglobulins in saliva and colostrum are primarily γ-globulins, most of which are different from those in plasma. In saliva, the predominant γ-globulin is one related to but different structurally from plasma γA [27] and colostrum contains not only a unique γA but also a γ globulin related to, but different from, plasma γG [28]. It is important to note that in such body fluids, the function of a given plasma γ-globulin such as virus neutralization which is normally a property of plasma γG may be assumed by the unique γ-globulin of the excretory organ, such as the γA of saliva or colostrum or the low molecular weight urine γ-globulins.

Normal maturation of immunoglobulin metabolism. The plasma concentration of γG in the normal adult is approximately 600 to 1,000 mg %. The antibodies found in γG include those which neutralize bacterial exotoxins and viruses and those which promote phagocytosis of bacteria. But the protection afforded by γG depends not only upon the antigenic experience of the individual, each exposure having the potential of stimulating the production of specific γG antibodies, but also the maturation of the γG synthesizing mechanisms. Although the human fetus has the capacity to synthesize detectable amounts of γG beginning by the sixth or seventh month of gestation, the amount synthesized is quite small, reaching only 0.1 to 1% of that in the adult per kilogram of body weight at the time of birth [29 30]. Yet, the normal infant at birth has a plasma concentration of γG which frequently exceeds that of the mother. Virtually all of the γG found in the full term new born is obtained from the plasma of the mother by transfer across the placenta [31 32]. This transfer is highly selective, since it is

not related to the molecular size of γG [31–33] and the permeability of the near term placenta for γG seems to be greater in the direction of mother to fetus than it is in the direction of fetus to mother [32] Many smaller proteins such as albumin which has a molecular weight of 65 000 orosomucoid with a molecular weight of 44 000 or pituitary growth hormone of molecular weight 35 000 do not traverse the term placenta nearly as readily as does γG [31] But the permeability of the placenta to γG is quite different at different stages of gestation. at six to seven weeks gestation, the fetal plasma γG concentration is but 50 to 100 mg and as late as 22 to 24 weeks gestation, it is only 100 to 200 mg% yet by 28 to 30 weeks of gestation the plasma concentration is only slightly lower than that at term indicating a relatively sudden selective increase in placental permeability to γG during the last part of the sixth and the early part of the seventh month of pregnancy [34] Beginning immediately after birth the plasma γG concentration falls with a half life of approximately one month (Figs. 1 and 2) since γG is catabolized like other proteins and synthesis by the newborn infant is quantitatively relatively insignificant The level of γG continues to fall until, by one to three months of age the rate of synthesis has increased to the point where the amount of γG synthesized becomes equal to the amount being degraded (Fig 2) and the plasma γG level stops falling [35] at this point the plasma γG concentration is approximately 300 to 000 mg%, being partly of maternal origin and in part of endogenous origin. Synthesis by the infant increases with time and the plasma γG

TABLE 2. *Immunoglobulin synthesis*

Clinical status	γG	γA	γM
A. *With adequate numbers of small lymphocytes*			
Normal individual	+	+	+
Agammaglobulinemia	−	−	
Dysgammaglobulinemia Type 1 (γG γA deficiency)	−	−	
Dysgammaglobulinemia Type (γA γM deficiency)	+	−	−
Dysgammaglobulinemia Type 3 (γG deficiency)	−	+	+
Dysgammaglobulinemia Type 4 (γM deficiency)	+	+	−
Found in normal or in Ataxia Telangiectasia (γA deficiency)	+	−	
(Not yet reported) (γG γM deficiency)	−	+	−
B *With thymic alymphoplasia with lymphop*			
Gitlin & Craig (67)	−	−	
Kenelof *et al* (79)	+	+	
Fireman, Johnson & Gitlin (80)	−	−	

concentration rises until by one to t years of age the child has a concentratı of γG comparable to that in the adult

It should be clear that the protectı afforded by γG in the newborn infan whether full term or prematurely bor is dictated by the nature of the antibodı present in the mother Thus, if the mothe has γG antibodies against diphtheria toxı or against measles, the infant born at ı time after seven months gestation wıl have concentrations of these antibodie approximately equal to those in the maternal circulation. After birth these maternally derived antibodies will be degraded with a half life of about one month as was noted for the total plasma γG If in a hypothetical instance a mother had a plasma concentration of γG anti measles antibodies which in an otherwise nonimmune person was 32 times that necessary to confer passive immunity the infant

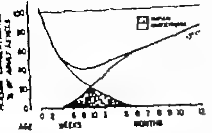

Fig. 2. The change in plasma γG concentration during the first year of life as the net balance between degradation of γG obtained from the mother and the synthesis of γG by the infant.

at birth would have a similar titer by one month of age, however the specific γG antibody titer would fall to half that present at birth and in each succeeding month, the titer would fall to half that in the preceding month, by five months of age, the titer would be approximately 1/32 that at birth or just enough to confer protection, but after five months of age the amount of anti-measles antibody left would be too low for adequate passive immunity. On the other hand, if the mother had anti-measles antibodies in a concentration just adequate to confer passive immunity the infant of that mother would have little γG protection against measles soon after birth despite the presence of almost adult γG concentrations. An infant passively protected against measles with γG may still acquire the infection when exposed to the virus, but clinical symptoms may not be evident and the infection may stimulate endogenous antibody synthesis, under such circumstances, passive immunity is converted to active immunity against measles. Thus, in the infant protected against measles during the first months of life by transfer of maternal γG *in utero*, exposure to measles during the passive immune period can lead to permanent immunity without clinical measles appearing at any time. Since the infant does not synthesize significant quantities of γG until one to three months of age specific γG antibody synthesis occurs primarily after one to three months of age but the amount of specific antibody needed for protection against measles is so small, that theoretically at least, even the small amount of γG synthesized by the infant before one month of age, can, with proper stimulation, have sufficient measles antibody to offer significant protection.

The infant at birth normally has little or no γM, yet the human fetus can, and does when stimulated antigenically synthesize specific γM antibodies beginning as early perhaps as three to four months gestation. By the time of birth, a relatively large proportion of the γM synthesizing capacity is operative but still inactive. With birth, and stimulation from the environment, γM synthesis rises rapidly (Fig. 1) the plasma γM concentrations reaching half of adult levels by three months of age [16, 27].

Antibodies which are γM proteins do not readily traverse the placenta at any time during pregnancy. Since most of the bactericidal activity of plasma against Gram-negative bacilli is due to specific γM antibodies acting in conjunction with complement, the deficiency of γM in the infant at birth represents a concomitant deficiency of such bactericidal antibodies [38]. This may have a significant bearing on the marked susceptibility of the infant to serious infections with Gram negative bacilli during the newborn period. Some mothers, due to repeated antigenic stimulation, can synthesize a small fraction of

not related to the molecular size of γG [31–33] and the permeability of the near term placenta for γG seems to be greater in the direction of mother to fetus than it is in the direction of fetus to mother [32] Many smaller proteins such as albumin which has a molecular weight of 65 000 orosomucoid with a molecular weight of 44 000 or pituitary growth hormone of molecular weight 35 000 do not traverse the term placenta nearly as readily as does γG [31] But the permeability of the placenta to γG is quite different at different stages of gestation. at six to seven weeks gestation the fetal plasma γG concentration is but 50 to 100 mg and as late as 22 to 24 weeks gestation, it is only 100 to 200 mg %, yet by 28 to 30 weeks of gestation, the plasma concentration is only slightly lower than that at term indicating a relatively sudden selective increase in placental permeability to γG during the last part of the sixth and the early part of the seventh month of pregnancy [34] Beginning immediately after birth the plasma γG concentration falls with a half life of approximately one month (Figs. 1 and 2) since γG is catabolized, like other proteins, and synthesis by the newborn infant is quantitatively relatively insignificant The level of γG continues to fall until, by one to three months of age the rate of synthesis has increased to the point where the amount of γG synthesized becomes equal to the amount being degraded (Fig 2) and the plasma γG level stops falling [35] at this point the plasma γG concentration is approximately 300 to 600 mg % being partly of maternal origin and in part of endogenous origin. Synthesis by the infant increases with time and the plasma γG concentration rises until by one to two years of age the child has a concentration of γG comparable to that in the adult.

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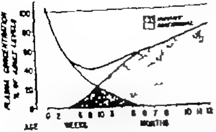
It should be clear that the protection afforded by γG in the newborn infant, whether full term or prematurely born is dictated by the nature of the antibodies present in the mother Thus, if the mother has γG antibodies against diphtheria toxin or against measles the infant born at a time after seven months gestation will have concentrations of these antibodies approximately equal to those in the maternal circulation. After birth these maternally derived antibodies will be degraded with a half life of about one month as was noted for the total plasma γG If in a hypothetical instance a mother had a plasma concentration of γG anti measles antibodies which in an otherwise non immune person was 32 times that necessary to confer passive immunity the infant



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The infant at birth normally has little or no γM, yet the human fetus can, and does when stimulated antigenically synthesize specific γM antibodies beginning as early perhaps as three to four months gestation. By the time of birth, a relatively large proportion of the γM synthesizing capacity is operative but still inactive. With birth and stimulation from the environment, γM synthesis rises rapidly (Fig 1) the plasma γM concentrations reaching half of adult levels by three months of age [36, 37].

Antibodies which are γM proteins do not readily traverse the placenta at any time during pregnancy Since most of the bactericidal activity of plasma against Gram-negative bacilli is due to specific γM antibodies acting in conjunction with complement, the deficiency of γM in the infant at birth represents a concomitant deficiency of such bactericidal antibodies [38]. This may have a significant bearing on the marked susceptibility of the infant to serious infections with *Gram-negative* bacilli during the newborn period. Some mothers, due to repeated antigenic stimulation, can synthesize a small fraction of

the total plasma bactericidal antibodies as γG the latter of course can traverse the placenta and under these conditions the infant is born with a small amount of γG bactericidal antibodies. But although many γG antibodies against Gram negative bacilli can be detected in maternal serum by hemagglutination and other related tests, and hence can be found in the newborn s plasma as well such antibodies have little or no bactericidal activity against the same organisms *in vitro* On the other hand the failure of transplacental transfer of γM can have certain beneficial aspects the α and β-isohemagglutinins present in normal plasma are primarily of the so-called natural or saline-precipitating type and these are γM proteins such maternal antibodies regardless of titer do not readily cross the placenta to affect a fetus whose ABO type is incompatible with that of the mother [39] Since some anti Rh antibodies are γM proteins, the maternal anti Rh titer alone is not necessarily an adequate guide to the amount of antibody passing to the fetus [39] Those hemagglutinins which do traverse the placenta are γG proteins and these most often appear as a consequence of immunization with incompatible erythrocytes.

Maternal plasma γA and γD immunoglobulins do not cross the placenta although the molecular weights of these proteins are similar for the most part, to that of γG nor does the conceptus synthesize these proteins. Consequently the infant is born lacking these antibodies as well, which in some ways can be a blessing most of the reagins responsible for immediate hypersensitivity reactions such as the wheal and flare response hayfever allergic asthma and the like are γA proteins [40 41] as are some isohemagglutinins. Blocking antibodies are usually γG proteins, and, of course do cross the placenta The synthesis of γA becomes evident beginning about two weeks after birth, but the plasma levels may not reach those of adults or approximately 90 mg % (Table 1) until the child reaches two to four years of age The maturation of γD synthesis remains to be clarified, and even less is known of the synthesis of the low molecular weight γ globulins.

The maturation of immunoglobulin synthesis is the product of the differentiation and maturation of those cells responsible for that synthesis. And the heterogeneity of molecular structure of the immunoglobulins is reflected in the biochemical heterogeneity of those cells which synthesize them The cells responsible for γG globulin production are primarily cells of the so-called plasma cell series, although there is evidence to indicate that γG synthesis also occurs in cells morphologically indistinguishable from lymphocytes, and some γG synthesis is apparent in cells found in germinal follicles of the lymphoid tissues [42–45] On the other hand, γM synthesis has been shown to take place in lymphocytoid cells [45 46] similar to those predominant in Waldenström s macroglobulinemia which do not develop into plasma cells and appear to be a separate cell line [46] Similarly γA is formed in cells which do not synthesize γM or γG but these cells are morphologically indistinguishable from the cells producing the latter proteins [47 48] A cell synthesizing one class of immunoglobulins does not synthesize another immunoglobulin class and there is evidence to indicate that

a given cell will synthesize molecules of only a single genetic type despite the number of different types that may be synthesized by a single person [15 49]. In fact, it would even appear that a given cell can synthesize only one antibody or molecules of a single specific structure, and at most only two or three different antibodies, indicating that each immunoglobulin synthesizing cell has a limited active DNA RNA code for antibody synthesis [50 51]. The plasma concentration of a given immunoglobulin can be correlated, qualitatively at least, with the numbers of specific immunoglobulin producing cells in the tissues.

Since γG synthesis does not materially increase in the human infant until approximately one to three months of age and since the γM synthesizing mechanisms are capable of stimulation at the time of birth, it is evident that the normal infant given such antigens as pertussis vaccine or diphtheria and tetanus toxoids at birth can synthesize specific antibodies and that these antibodies would primarily be γM proteins. Dancis and his colleagues have shown that the antibody response in the newborn stimulated antigenically at birth is somewhat delayed compared to a similar injection in a child of several months, or seven to ten days after injection as compared to three to four days, and that it is quantitatively smaller. Thus, although small, the amount of antibodies produced by antigenic stimulation at birth confers a degree of protection otherwise absent and can provide an immunologic sensitization or memory for succeeding injections of the same antigen; a second injection in the same infant at one month of age, for example can result in a greater and more rapid synthesis of specific antibodies than a first injection in an infant of the same age. The presence of significant amounts of specific maternal γG antibodies in the infant at birth, however may directly or indirectly influence the effectiveness of immunizations begun at birth. Infants possessing maternal diphtheria antitoxin at birth can, nevertheless, produce diphtheria antitoxin in response to diphtheria toxoid at least half as well as infants born without such antibodies as has been shown by Dancis, and with time the levels of antitoxin in the two groups of infants will be similar. This may be attributed to the observation that specific γM antibody synthesis may be inhibited by the presence of γG antibodies of similar specificity: under these circumstances, the synthesis of specific plasma antibodies will be delayed and will rise more slowly than in newborn infants without such maternal antibodies until the γG system matures further. The presence of relatively high concentrations of specific maternal γG antibodies can prevent effective vaccination *with some live viruses*, such as the modified polio viruses, by impeding even subclinical infection and thus prevent adequate antigenic stimulation.

Careful study of the sequence of antibody synthesis has revealed that, in children or adults, γM antibodies are the first to be detected in response to a specific antigenic stimulus followed by γG antibodies [52]. It will be noted from Table 1 that the molar rate of γG synthesis is approximately 20 to 30 times that of γM, however the effectiveness of γM in those detection tests commonly used, such as hemagglutination, is several hundred times that of γG. As a consequence of these

data, the apparent temporal sequence of γM and γG antibodies can be explained on the basis of the kinetics of separate molecular species rather than any transformation of synthesis from one type to the other the γM antibodies appear to be synthesized first, because of their greater effectiveness in the detection system In young infants, the apparent temporal γM to γG sequence is greatly exaggerated, also a matter of kinetics since the maturation of γM synthesis occurs earlier than γG synthesis. some antigens such as typhoid H antigen, stimulate the synthesis of primarily γG antibodies in older children but in the young infant, anti typhoid H antibodies are predominantly γM proteins on the basis of hemagglutination or hemolysis tests. Some antigens it should be noted do not stimulate much specific γG synthesis. the principal antibodies formed to typhoid O antigen, for example from young infants to adults, are γM proteins.

Deficient immunoglobulin synthesis If the synthesis of each of the three major immunoglobulins γG γA and γM is considered to be an independent variable the simple presence or absence of each of these proteins would result in eight different phenotypes (Table 2) Seven of these possibilities have been described [53–59] and of the six known anomalous states at least four have been shown to be hereditable and one of the latter agammaglobulinemia, is attributable to more than one genotype [60–63] Those conditions characterized by a deficiency or absence of γG synthesis alone or in combination with other immunoglobulin deficiencies are associated with severe recurrent bacterial infections, usually pulmonary deficient synthesis of both γA and γM (type 2 dysgammaglobulinemia) is also associated with recurring infection. However deficiencies of either γA or γM alone without other associated immunoglobulin deficiencies are frequently but not invariably found to be accompanied by such infections and such synthesis deficiencies may occur in otherwise immunologically normal individuals [36 59 63]

One disorder of immunoglobulin synthesis, agammaglobulinemia occurs in at least three different forms: (1) a congenital form the onset of infections beginning in infancy or early childhood, (2) a form frequently referred to as acquired or adult agammaglobulinemia, and (3) a transient condition which occurs in infants beginning at two to three months of age The congenital form can be differentiated into two conditions. (1) a sex linked recessive characteristic occurring in males and transmitted by the female, and (2) a condition found in female infants. The congenital disorder found in the female may represent the younger portion of the age spectrum which is associated with the so-called acquired or adult form the onset of infections in adult agammaglobulinemia occurs at any age from 7 to 70 years, but it is found in both males and females. Despite a lack of documentation of the hereditary nature of agammaglobulinemia in some male infants with the disorder there is great temptation to classify the condition in male infants nevertheless, as the sex linked recessive form and to relegate female infants with agammaglobulinemia into a separate category if the latter female infants do indeed represent one end of the age spectrum of the adult form of the disease then some of the male infants may have been misclassified In

view of the fact that relatively few siblings of patients with adult agammaglobulinemia appear to develop agammaglobulinemia as compared to siblings of patients with sex linked congenital agammaglobulinemia, the distinction is of some prognostic importance to the remainder of the family. Unfortunately at the present time, it is not possible to distinguish between the male infant with the sex linked disorder and the hypothetical male infant who may have a less penetrable genetic state as in adult agammaglobulinemia.

The consequence of deficient immunoglobulin synthesis as exemplified by the agammaglobulinemic state is a marked susceptibility to recurrent serious infections, *primarily bacterial*. In most instances the lungs are the most frequent area of serious attack, but meningitis and septicemia are also frequently observed. In most instances, the agammaglobulinemic state is not absolute and some γ-globulin synthesis does occur: the overall γG range found in this condition, for example, is from 0 to 100 mg %, and in the congenital form it is usually 10 to [illegible] mg %. Small quantities of neutralizing antibodies against some viruses can be demonstrated [64] and in the case of measles at least, the theoretical amount of specific antibody synthesized would seem to be enough to confer protection [62]. In addition, immunity against some viruses such as vaccinia and varicella appear to be dependent for the most part upon a biochemically intact lymphocyte population and in most agammaglobulinemic individuals the lymphocytes retain their capacity to synthesize cellular antibodies [61, 62, 65, 66]. Consequently viruses do not seem to play any more havoc in the agammaglobulinemic individual without lymphopenia than in the normal person, the agammaglobulinemic person who recovers from a viral infection usually demonstrates a normal resistance against reinfection with the same virus unless the disorder is accompanied by lymphocytic hypoplasia. As would be expected, all of the lymphoid tissues in the agammaglobulinemic without lymphocytic hypoplasia reveal a marked deficiency or complete absence of plasma cells and the virtual or complete absence of cells capable of synthesizing any of the other immunoglobulins as well, in addition, the lymph nodes, spleen and gastrointestinal tract have virtually no germinal follicles. Although the thymus is *dysplastic, it is quite* what would be expected in the child afflicted with repeated life-threatening infections, and contains both lymphocytes and Hassall's bodies [67]. Interestingly, the lymphoid tissue represented by the tonsils and adenoids is absent, nevertheless, the lymphoid tissues with the exception of the tonsils and adenoids, have a relatively normal complement of small lymphocytes, and the peripheral or circulating lymphocytes are normal in both number and apparent specific function.

There are conditions which are distinguished by *deficiencies in the synthesis of* a specific antibody without any obvious decrease in overall immunoglobulin synthesis. In children with leukemia or cystic fibrosis, for example, and occasionally in a normal child as well, measles virus may cause fatal giant cell pneumonia associated with an absence of neutralizing or complement-fixing antibodies against the virus [68]. Progressive vaccinia has in some instances been associated with an absence

of anti vaccinia antibody synthesis. But it should be cautioned that the absence of specific antibodies in both of the situations just described is not necessarily related to the failure in resistance against the specific virus. In the case of children with leukemia or cystic fibrosis who develop measles giant cell pneumonia pooled γG which contains anti measles antibodies fails to check the measles virus and in progressive vaccinia, the principal deterrent to the infection is not specific humoral antibody but cellular antibodies formed in lymphocytes. Another example of a specific antibody deficiency is the absence of isohemagglutinins in the Wiskott-Aldrich syndrome but the relation between the disease and the deficiency has not been clarified.

Transient hypogammaglobulinemia is attributable to a delay in the onset of γG immunoglobulin synthesis beyond one to three months of age [60] Since γG obtained from the mother is degraded, under these circumstances the γG concentration in the infant will fall below 150 mg% by the time the infant is two to five months of age and the child will be vulnerable to serious bacterial infection. Fortunately the failure in γG synthesis is temporary and by the time the child is 7 to 15 months of age significant γG synthesis becomes apparent It has been postulated that this form of hypogammaglobulinemia is due to an incompatibility of γG Gm types between mother and fetus with synthesis of maternal antibodies against the Gm type of the fetus: although most anti Gm antibodies are γM proteins, on rare occasions they may be γG and could therefore pass the placenta from mother to fetus [30 60] The theory requires that such maternal antibodies would suppress those fetal cells synthesizing the specific Gm molecule. The theory remains to be proven but there is considerable evidence in animals to give it plausibility

The Thymus and the Lymphocyte

The most readily observed manifestation of cellular antibody synthesis is the dermal delayed hypersensitivity reaction, a specific induced sensitivity to an antigen which is demonstrated by the intradermal injection of the antigen and manifested by an area of erythema which appears usually within 12 hours, reaching a maximum within 48 hours after injection and subsides gradually sometimes taking several days or more to disappear This type of reaction is also exemplified, however by the sudden exudative reaction in primary pulmonary tuberculosis that may occur in one to two weeks after infection and by the sudden extension of erythema and induration around the site of vaccinia inoculation at seven to ten days after the vaccination, both are specific reactions against antigens at the tissue site mediated by cellular antibodies As is clearly shown by the work of Waksman and his co-workers, the cell responsible for the synthesis of such cellular antibodies is the small lymphocyte. The delayed type of hypersensitivity to a specific antigen can be transferred to a nonsensitive recipient by means of peripheral cells in the circulation of a sensitive donor or by means of cells from lymphoid tissues of the donor it cannot be transferred by means of plasma in contrast to the immediate or wheal-and flare type of hypersensitivity which is attributable to humoral antibodies. The delayed type of hypersensitivity

to specific antigens can also be transferred to nonsensitive recipients by means of extracts of sensitized lymphocytes [70–72] or by means of a transfer factor [73] isolated from such extracts, the factor having a molecular weight of 700 to 4000 and containing nucleic acids [74]. The transfer factor apparently passively sensitizes the recipient's lymphocytes and, once induced, the hypersensitivity may last from weeks to months depending upon the amount of factor used. Passive transfer with sensitized viable lymphocytes can induce hypersensitivity which may remain for years.

By eight to ten weeks gestation, lymphocytes are present in the blood and tissues of the human embryo. By the time of birth, the lymphoid tissues are well populated, though certain areas, such as the appendix, do not have nearly as many lymphocytes as will be present within the year and the lymph nodes lack both primary and secondary follicles. By three months of age primary follicles may be evident as well as an occasional germinal follicle, and by one year of age the architecture of the lymphoid tissues is similar to that in the adult. There are, however, several populations of lymphocytes, the differentiation of the small lymphocyte appears to be related to normal development of the thymus, but some lymphocytes which morphologically appear as medium or large lymphocytes are not under thymic control. The peripheral lymphocytes come from the lymphoid tissues and at least two groups of lymphocytes can be distinguished: one group which appears to arise primarily from lymph nodes, the spleen and the gastrointestinal tract, and another which comes from the bone marrow restricted areas of the spleen and the appendix. The lifetime of the peripheral lymphocyte, at least in the adult, is at least one year and more likely two years.

The role of the lymphocyte in preventing infection in man is best observed in the condition thymic alymphoplasia, a failure in the development of the thymus as manifested by a primitive thymus which is made up principally of reticulum cells, has no Hassall's bodies and is virtually devoid of lymphocytes [67, 75–78]. Patients with thymic alymphoplasia also have lymphocyte hypoplasia, or a marked paucity of lymphocytes in all lymphoid organs, including the tonsils and adenoids, and most demonstrate alymphocytosis or a lymphopenia below 1500 cells per cu. mm. The development of the thymus, and hence the small lymphocyte, is independent of the development of the immunoglobulin synthesizing cells [79, 80], so that patients with thymic alymphoplasia may have normal rates of immunoglobulin synthesis or may show deficiencies in the synthesis of one or more immunoglobulins (Table 2).

The presence of persistent lymphopenia is a suggestive aid in the diagnosis of thymic alymphoplasia, but it must be emphasized that some patients have normal blood lymphocyte counts. A lymph node biopsy or a rectal biopsy carefully studied is probably the most reliable single diagnostic aid. The peripheral lymphocytes do not repopulate the lymphoid organs, including the thymus.

Thymic alymphoplasia thus far has invariably terminated fatally, usually within the first two years of life [67, 75]. Children with this disorder, with or without associated immunoglobulin deficiencies, are

afflicted with almost intractable continuous infection In almost all instances pulmonary infections dominate the clinical picture but intestinal infection, and systemic or oral moniliasis play a significant part in many At some point during the course of the disorder an exanthem is seen in some These children cannot actively develop delayed hypersensitivity since they lack small lymphocytes, but they can be passively sensitized using viable lymphocytes from a sensitive donor [66] Interestingly they do not reject skin grafts. Thymic alymphoplasia is transmitted either as a sex linked autosomal recessive characteristic appearing in males or as an autosomal recessive occurring in both males and females. The course of this disorder is not ameliorated with pooled γG therapy

Thymic alymphoplasia has been also found in a rare condition known as reticular dysgenesis a state characterized by alymphocytosis, agranulocytosis, lymphocytic hypoplasia and an absence of granulocyte precursors in the bone marrow These children have died of overwhelming infection soon after birth [77 78]

Any attempt to relate the differentiation of the lymphoid and immunoglobulin systems in a coherent fashion certainly requires far more evidence than is now available But on the basis of studies of abnormal lymphocyte and immunoglobulin synthesis, a vague picture appears to be emerging To theorize then, on the basis of such evidence as has been referred to in this discussion, the pattern of cellular differentiation in Fig 3 is offered It will be noted that the failure of differentiation of primitive cell *A* would result in thymic alymphoplasia and agranulocytosis as

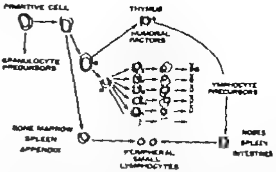

Fig 3 A proposed scheme of the differentiation of immunologically competent cells responsible for synthesis of the specific immune factors. On the basis of the immunological deficiency disorders discussed in the text, the differentiation sequence from primitive cell *A* to cell *C* presumably takes place before 8 to 10 weeks gestation. The differentiation of cell *D* to cells *E* to *J* or the differentiation of cells *E* to *J* to immunologically competent cells would appear to take place at different later periods of gestation, cell *G* having differentiated by 12 weeks gestation and cell *E* by 24 to 28 weeks gestation.

noted in reticular dysgenesis, whether or not agammaglobulinemia is also a part of the picture of reticular dysgenesis as predicted by this scheme is not known. Failure of cell *B* to develop would presumably result in thymic alymphoplasia and agammaglobulinemia with alymphocytosis whereas failure at the level of cell *B′* would result in thymic alymphoplasia and agammaglobulinemia without alymphocytosis. Failure of cell *C* to differentiate would result in thymic alymphoplasia with relatively normal immunoglobulin synthesis rates, whereas failure in cell *D* would result in agammaglobulinemia without thymic alymphoplasia It was pointed out at the beginning of this discussion that the different plasma immunoglobulins are synthesized in different cells and that each cell synthesizes only a single or at most a limited number of different immunoglobulin molecular structures For simplicity the differentiation of only the individual

immunoglobulin classes based on the synthesis of different heavy chains is depicted in Fig 3 but it is recognized that the cells of each class differentiate further to the point where only *one to three* different antibodies are synthesized per cell. Failure of one or more but less than all, of the cells synthesizing the individual γ-globulin classes would result in dysgammaglobulinemia.

An attempt has been made here to correlate some of the generally accepted present concepts *of the structure* function and *metabolism* of antibodies in relation to the pattern of immunity against infection manifested at various stages of human development But if any truth is absolute it is that the future will undoubtedly prove the present *to be at least partly if not* entirely wrong

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Main Features of the Congenital Nephrotic Syndrome

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The congenital nephrotic syndrome or congenital nephrosis (CN) is a rare disease showing signs of lipoid nephrosis already at birth or at least in the course of the first few weeks of life [2, 4, 5, 6 7 22]. In Finland CN is much more common than anywhere else. That has been a natural impetus for comprehensive studies on CN in this country [6 7 8, 9 10 12, 13 14, 16, 17 19 21].

Though CN greatly resembles the acquired form of the idiopathic lipoid nephrosis of childhood, it has, however several pathognomonic or characteristic symptoms and signs. CN is a familial disease. In most cases the intrauterine onset of the disease is clearly evident

1 Nearly unexceptionally the placenta is very large i.e more than 25 per cent of the birth weight [12];

2. The birth weight is low which, at least partly derives from prematurity [6, 7 13];

3. Proteinuria and the nephroti serum protein pattern are seen immediately after birth in a great majority of cases [6 7 13];

4. Wide cranial sutures at birth indicate that the ossification process is delayed already *in utero* [8];

5. Polycythemia and especially the advanced erythroblastosis occasionally seen in neonatal CN patients probably derive from impaired function of the large edematous placenta [8].

The patients may show edema at birth or it develops in the course of the first few days, or occasionally weeks of life. Ascites and meteorismus often cause a marked bulging of the abdomen and the appearance of hernias in the more advanced cases. The patients usually lie in a position similar to opisthotonus. This is very probably due to the discomfort caused by the bulging abdomen. The ankles are very often flexed in the calcaneo-valgus position since birth. The cartilages are soft, which probably causes the peculiar face in CN (Fig 1)

CN is an unexceptionally fatal disease. Medication with corticosteroids seems to be *of no value*. The *physical development* is extremely poor Most of the patients succumb to infections at the age of *few* months. The longest life-span of a CN patient in Finland has been three years and 10 months. The biochemical findings of CN are principally similar to those of acquired lipoid nephrosis. One chemical characteristic of CN is the elevation of the gamma-M immunoglobulin. The renal function remains good in most respects [8, 12]

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Fig. 2. A map showing the distribution of the known CN families by countries up to 1966. A black dot indicates one CN family with one or more sick children.

Nearly one third of the marriages of CN parents are consanguineous, even if rather remote. A great number of close or distant relationships between several CN parents were disclosed. Thus, 10 CN parents could be shown to be descendants of one and the same ancestor pair living in the 18th century. The ancestry of CN patients was found to be concentrated in certain areas in the country. The recessive transmission associated with some peculiar genetic conditions of the population in Finland, dealt with in the study mentioned, seems to explain the abundant occurrence of CN in this country.

Though it is now known that CN is an inherited disease, the pathogenesis is still obscure. Whether the basic lesion in CN is a renal malformation [3, 17] or an inborn error in protein synthesis of the basal membrane of the glomeruli and perhaps in the synthesis of other proteins [16], or whether the frequent immunological features associated with CN play a causal role [12, 14, 15], remains to be clarified.

Summary

Until now 85 patients with an evident congenital nephrotic syndrome have been recorded in Finland. The main features, incidence and etiology of CN are dealt with in this report.

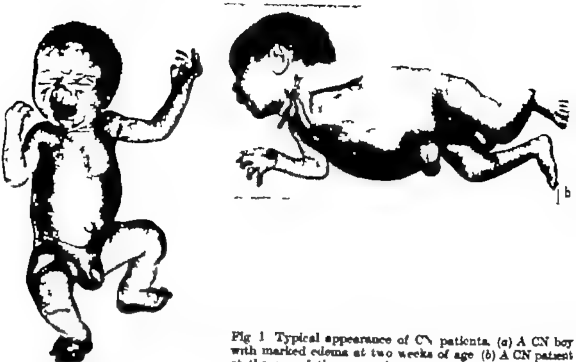

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Fig. 1. Typical appearance of CN patients. (a) A CN boy with marked edema at two weeks of age. (b) A CN patient at the age of three months. Note the bulging abdomen, hernias and the opisthotonic position.

Patho-anatomically the most prominent changes are seen in the kidneys. They are large and pale and show microcystic dilatations of the proximal tubuli, often a swan-like neck, and regularly glomerular changes. These consist of proliferation of glomerular cells, crescent formations, the presence of polymorphonuclear leukocytes, and thickening of the capillary walls. By electron microscopy the most constant findings are fusion of the foot processes of the epithelial cells and nodular thickening of the endothelial side of the capillary basement membrane [3, 5, 7, 8, 9, 10, 17, 21, 22]. Round cell infiltrations are often seen in the kidneys and the heart. The liver and the spleen often show signs of erythropoesis. Interstitial pneumonia is a common finding at autopsy [8, 15].

The occurrence of evident CN families known to us in the world is presented in Fig. 2. Though there are 46 reported CN families from 17 other countries [1, 2, 3, 4, 5, 11, 15, 18, 20, 22, a complete list is given in reference 16], the accumulation of CN in Finland is striking. Finland has a population of about four and half million. Until now 85 Finnish CN cases from 66 families have been detected. The mean annual number of verified CN children born in Finland in the last ten years has been seven, which roughly gives the rate of one CN child per 10 000 deliveries.

Recently a genetic study [16] on the comprehensive Finnish family series has given definite evidence in favour of an autosomal recessive transmission of CN. Thus, the corrected proportion of affected siblings is very close to the theoretical value of 0.25 (0.250 according to complete truncate ascertainment in families whose parents were married in 1950 or later).

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From the New York University New York, U.S.A.

Some Reflections on Pediatric Teaching

by L. EMMETT HOLT JR.

It is a pleasure to contribute to a volume in commemoration of Professor Constantin Choremis—an outstanding pediatrician from every point of view who combined to a high degree the attributes of the clinician, the teacher and the investigator

In the course of the past 50 years in which I have been in medicine I have witnessed or participated in a number of techniques and experiments in medical teaching, and it occurs to me that it might be of interest to discuss them even though in the last analysis it is difficult to draw firm conclusions regarding their merits, for controlled studies of teaching procedures are not available.

When I first studied medicine during the time of World War I, the pattern of medical teaching in the United States was heavily influenced by European and particularly by German medicine—it might be called the Geheimrat pattern. The professor who did virtually all of the teaching of a clinical subject was a man on a pedestal Somewhat of a Czar his word was never challenged by any staff member He was, as rule the sole examiner of students. He was the repository of all knowledge in his specialty the possessor of an extensive private library to which few if any one else had access. He was an expert clinician and much sought after as a consultant. We owe a great debt to this group of people who were indeed the founders of pediatrics.

A different pattern developed, mostly after World War I, and has since become quite widespread. It was the era in which research became glamorous. Research in pathology there had been, but research on living subjects—clinical research, with the tools of biochemistry and immunology that was something new In time it affected the prestige of the pure clinician, skillfull though he might be. As knowledge advanced it was no longer possible—even in a branch of medicine such as pediatrics —for one man to encompass it all. Subspecialization in pediatrics began to grow in the late 20s and has been steadily on the increase since We now have and must have pediatric cardiologists, pediatric endocrinologists, pediatric hematologists, subspecialists in neonatal disease in neurology in pulmonary physiology in many other branches of disease. It is impossible for one man to keep up with the continuous

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Some Reflections on Pediatric Teaching

by L. EMMETT HOLT JR.

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In the course of the past 50 years in which I have been in medicine I have witnessed or participated in a number of techniques and experiments in medical teaching, and it occurs to me that it might be of interest to discuss them even though in the last analysis it is difficult to draw firm conclusions regarding their merits, for controlled studies of teaching procedures are not available.

When I first studied medicine during the time of World War I the pattern of medical teaching in the United States was heavily influenced by European and particularly by German medicine—it might be called the Geheimrat pattern. The professor who did virtually all of the teaching of a clinical subject was a man on a pedestal Somewhat of a Czar his word was never challenged by any staff member He was, as a rule, the sole examiner of students. He was the repository of all knowledge in his specialty the possessor of an extensive private library to which few if any one else had access. He was an expert clinician and much sought after as a consultant. We owe a great debt to this group of people who were indeed the founders of pediatrics.

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spread of subspecialization. It is impossible to keep up with the enormous expansion of the literature and it has become increasingly difficult for one man to teach with the newer diagnostic techniques. The team approach has come. Departments of pediatrics have had to expand, have had to depend more and more on individuals with specialized knowledge. Libraries, too are now seldom private and access to new knowledge has become the right of the youngest physicians. It has brought a loss of prestige to the all-encompassing leaders. As they pass on, they are not being replaced by their likes; the prized individual is the man who can create knowledge rather than just dispense it. Leadership and personality there must be and organization. The professor of today needs to be a general who can organize an effective army—one who can effectively coordinate individual skills.

One characteristic thing about Americans is that they are always trying something new. This is true in teaching of pediatrics as well as of medicine in general. As pediatrics emerged as a respectable specialty, there was an urge to increase its status by acquiring more and more teaching hours for it in the curriculum. Questionnaires were circulated to the various medical schools. It fell to my lot to estimate the number of hours devoted to pediatrics at Johns Hopkins where I was at that time. Johns Hopkins was without much doubt the leading pediatric center at that time. Many distinguished pediatricians had been trained by Dr Howland including more than a dozen department heads, but it appeared that only 96 hours had been devoted to pediatrics as compared to a national average of over 200 hours. It was quality than quantity which counted.

A number of different techniq interest students in pediatrics have employed in our country. One w *catch the student early* even in his year when he is bored by anatomy perhaps depressed by the complexit biochemistry and show him some pediatric patients and that pediatrics a real live subject. I have participat several of these attempts. These prog were always popular with students, sooner or later all were abandoned. T took up too much faculty time an was eventually felt that unless a stu had enough imagination to know w was coming and to see the necessity putting his nose to the grindstone w his anatomy and biochemistry, he pr ably wasn't worth much.

Interdisciplinary teaching is someth that nearly every medical school has ex rimented with. The clinical-pathologi conference is, however, almost the o manifestation of this technique that h survived. The greatest interdisciplina teaching effort—one that is still going —is that employed in Cleveland at We tern Reserve Medical School. Teaching by organ or by system rather than by th familiar medical disciplines. A studen takes up the liver, dissects it, looks at i under the microscope, studies its func tions, poisons it and sees it in various dis ease states. Then he goes on to th spleen, the alimentary tract, the circula tory system, the lung, the nervous system, etc. He sits at one desk for his first two years. One drawer of this desk is his anatomy laboratory—an air conditioned drawer containing an infant's cadaver

Another drawer contains a microscope. A part of his desk rolls back to reveal a chemical laboratory—and so it goes. The plan seems to work well for the first two years and attempts are being made to extend it into the later years, though more difficulties have been encountered there. It appears that eventually the student at Western Reserve learns the same things as are taught in other medical schools, but in a different order. What has been gained is still an open question, but two positive items stand out: (1) Western Reserve has received a lot of money to carry out this experiment and (2) the experiment engendered considerable enthusiasm among teachers to make it work. It is hard to balance this up against possible deficits—time lost in reorganization, time taken from other functions of a medical school. The effort to revamp our conventional disciplines could, unless generally adopted, lead to administrative difficulties—to departments of hepatology or splenology rather than to departments of medicine, surgery and pediatrics, which would make it difficult for an individual to migrate from one school to another.

A general trend in American pediatric education has been the gradual replacement of the formal lecture given to an entire class by informal teaching to small groups. In some institutions formal lectures have been dispensed with altogether. This trend is, I think, sound and makes for better teaching. The difficulty is its cost in time. One year while I was at Johns Hopkins we decided to go all the way and abandon formal whole class exercises altogether. The 60 odd students were divided into 8 groups of 7 or 8 each and an instructor stayed with his group for the entire year giving them informal conferences once a week. There were real advantages in this plan. It made for a very intimate relationship between student and instructor. The difficulties were two—(1) the number of instructor hours devoted to teaching encroached to some extent upon the research activities of the staff, and (2) not all the instructors were equally talented as teachers; the groups assigned to younger instructors felt somewhat shortchanged as compared to the group fortunate enough to have the professor. It was an enjoyable teaching year but we abandoned it for these two reasons and went back to a hybrid course—part lectures and part informal conferences.

The content of a pediatric course is a much discussed subject. The enthusiastic teacher is bedeviled by the prospect that a student may graduate from medical school without knowing anything about this or that and pretty soon he wants the whole textbook covered. The student is faced with a great deal of memorizing much of which will be promptly forgotten and never used. It should be realized that one can't make pediatricians out of all medical students any more than one can make surgeons out of them. One can only expose them to pediatrics—its special problems and how they are approached. Only a *minimum* of factual knowledge is needed. How to think about a problem? How to approach it? What to do to find out more about it? These are the things that should be emphasized for students.

I have been to a number of conferences concerned with pedagogy—with techniques for imparting information to students. Of course the newer audiovisual techniques have been

are valuable but, by and large one must depend on traditional methods. There are good teachers and poor teachers. There is an inborn something in the good teacher that enables him to see into the student s mind. Someone who has it will not talk over the student s head nor will he bore the student There are however a few pedagogical tricks that can be learned My friend the late Paul Lamson, a professor of pharmacology used to watch the students very closely when he was lecturing and he learned how uniform and predictable their reactions were. If he wanted to catch the attention of the class all he had to do was to say now there are just three things about this that I want you to remember The students would all sit up straight, out would come the pencils and the note books. But if he said now I am going to take a few minutes to review for you the physiology of the kidney the students would lean back and relax. A happy medium alternating between these two techniques seemed to work best Continuous stimulation could not be maintained and there had to be periods of relaxation.

In clinical teaching the instructor who can make diagnosis a game has a great asset. By giving out limited information and withholding some he can make the student consider a wider spectrum of possibilities. A bandage can be put on to conceal a tuberculin reaction or the site of a lumbar puncture to make the discussion more interesting before the final and perhaps dramatic denouement There is an advantage in teaching by the Socratic method—asking the student questions that will make him think. I can recall one of my teachers—this time a neurologist—who had no objections to faking a lectu demonstration to illustrate a point If h had no patient on whom he could de monstrate a tabetic gait or the hyperactiv reflexes of general paresis he would trai one to perform. The important thing i his opinion was to leave the typical pi ture in the student s mind.

There are bad pedagogical technique too The instructor who assigns fixed reac ing from a textbook and conducts a qui with the book on his lap fails to inspire hi class. He is bored and so are they

When I was about to leave Baltimor some 20 years ago to take over a pediatr department of my own in New York went first to my chief Dr Park, wit whom all of us had a close filial relation ship, and asked him what he thought should do about teaching His reply sur prised me and may surprise some others He said. 'You don t have to do anythin about it I have come to the conclusio that it takes care of itself Your job is t create knowledge not to pass along dog mas that are traditional and that may b wrong If you produce new informatio you will find that there is always someon in the department—some born teacher— who will tell the students about it. New knowledge is thrilling It makes a dyna mic rather than a static department It puts a premium on the open mind.

A similar thought in slightly different form was expressed by the late Alan Gregg head of the medical division of the Rocke feller Foundation and one of the greatest of our medical philosophers. 'The real purpose of a medical school he said is the education of the faculty I used to hang that quotation on my wall Research means better medical care and better

teaching. The fruits of new work are passed on to the patient. The man who contributes them becomes a better clinician in this area, his teaching becomes the teaching of an expert. This, in a nutshell, is my own philosophy It is the philosophy I have tried to live by in my years at New York University

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From the University of Sheffield Department of Child Health.
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Restrictive Practices in Paediatrics

by R S ILLINGWORTH

To some extent all children need restriction in their activities. They have to be protected from danger until they are old and mature enough to become independent of supervision All children need to learn discipline they have to learn to conform to custom, to respect the property of others, to behave in a way acceptable to others. All children need to learn to accept a No Some children have to suffer restrictions in their diet either because of a metabolic disease or because of threatening obesity Throughout their childhood and in early adolescence restrictions are necessary decreasing as maturity is reached. This article however is concerned with some undesirable restrictions.

Infant Feeding

After prolonged disagreements about the desirability or otherwise of feeding premature babies early in the first 24 hours, or of delaying feeds for 48 to 72 hours many are now realising that there are distinct advantages in early feeding and disadvantages in starvation. Ylppo of Finland [32] has for many years advocated early feeding He argued that rats tolerate early starvation badly and die within 24 hours. Infants rapidly become acidotic if starved. Several workers have found that delayed feeding of premature babies is associated with a higher serum bilirubin. Hubbell et al [12] studied 48 infants of diabetic mothers, feeding half in the first 24 hours and half after 48 hours. Those fed early had a lower indirect bilirubin than those fed late Smallpeice & Davies [20] working at Oxford, provided further evidence for the desirability of early feeding of premature babies. It now seems clear that early feeding reduces the risk of hypoglycaemia reduces the tendency to acidosis, and keeps the serum bilirubin lower than delayed feeding—all important advantages.

It has long been our practice to feed premature babies about 12 hours after birth. We never found it easy to believe that a delay of 48 to 72 hours would make the baby so much more mature that regurgitation was less likely—and that is one of the main arguments advanced by the proponents of late feeding

We have always advocated self demand feeding of babies in Sheffield Yet there are still some who claim that babies should be fed on a rigid schedule and denied a feed in the night if they awaken and cry for it In the Jessop Maternity Hospital, Sheffield, where the babies are in a crib

at the mother's side, all babies are fed on the self demand method. It is far easier for the nursing staff to supervise feeds where necessary and it greatly reduces the amount of crying.

It is irrational to instruct mothers to feed the baby for an exact time on each breast (usually ten minutes). This ignores the fact that babies differ in the rapidity with which they suck, that nipples vary and that breasts vary with regard to the rapidity of the flow of milk.

There are still many doctors who ascribe vomiting, crying or diarrhoea to overfeeding and then restrict the amount of feeds. I am firmly convinced that overfeeding in a young baby is a myth. Babies know when to stop, just as lambs, calves and other animals do. I have never seen lambs or calves vomiting as a result of overfeeding. It would be strange if they knew when to stop, while human babies did not. I strongly believe that young babies should be given as much as they want.

There is no justification for laying down the exact age at which a child should be weaned on to thickened feeds. If it is thought desirable thickened feeds can be given to three or four week old baby.

Special diets have to be given to children with such metabolic defects as phenylketonuria, leucinosis, galactosaemia, fructose or sucrose intolerance, hypercalcaemia, and coeliac disease and dietetic restrictions are necessary for all these conditions, and for certain similar disturbances. Dietetic restriction is unjustified, however for many conditions for which restrictions are still applied by many. Examples are infective hepatitis and nephritis.

Crews & Faloon [4] showed the fallacy of giving a low fat diet in liver disease and reviewed the literature. It has always been our practice to give children with infective hepatitis a normal diet with unrestricted fat unless they wished to have a low fat diet, which is unusual. Nefzger & Chalmers [21] have shown that a high protein diet shortens the duration of illness.

I see no reason to restrict the protein in diet for acute nephritis, unless there is severe oliguria, which is rare, in children. We conducted a controlled experiment with low protein and high protein diets, [13] and found no difference in the rate of healing. Neither do we see the need for the restriction of fluid or salt in acute nephritis except in the rare cases of severe oliguria. It is unpleasant for the child and achieves nothing. It is quite irrational.

In the case of gastroenteritis and diarrhoea, opinions differ about the need for dietary restriction. Holt [10] has long advocated normal milk intake in infantile gastroenteritis. Mitchell *et al.* [20] studied 396 cases of diarrhoea, comparing the effect of early feeding with the usual starvation. Those fed with milk did as well as the starved ones. O Keefe [22] conducted a similar study and found that babies given milk had more bulky stools, but absorbed more and did as well or better than those babies which were starved. In the case of ulcerative colitis, however Wright & Truelove [31] have shown by controlled experiments that a milk free diet is of value in some patients.

In treating an older child with diarrhoea (e.g. due to dysentery) I would not restrict the diet. I find it difficult to believe that when the intestinal contents are liquid or semiliquid, as they are the avoidance of ordinary solid food can possibly make any

difference to the course of an attack of diarrhoea

With regard to diabetes, there is a legitimate difference of opinion about dietary restriction. One must do anything possible to reduce the high incidence of arterial changes after a few years and Wilson *et al* [29] showed how poor control of childhood diabetes is followed by a higher incidence of arteriosclerosis. Payne & Forsyth [23] however followed 100 diabetic children given a free diet and found that the incidence of arteriosclerosis was as low as or lower than that described by advocates of rigid dietary restriction.

There is no justification for giving a fat free diet for the periodic syndrome (migraine) or for urticaria The latter is far more likely to be due to sensitivity to insect bites than to food allergy which is a rare cause of urticaria

Fig. 1 Swaddled baby in a Leningrad Hospital

Physical Restriction

Swaddling of babies is still practised in some quarters A few years ago I visited Russia and was interested to see all babies in the hospitals and coming up to the hospitals tightly swaddled. In an excellent review of the subject Lipton Steinschneider & Richmond [18] discussed the origin of swaddling and the probable reasons for it. These included the prevention of masturbation, pacification, and an attempt to keep the legs straight. They found in experiments that swaddling does in fact reduce the amount of crying in babies. There is no evidence that swaddling does harm, though one feels some revulsion against the practice

In the past restrictive methods were used for the treatment of masturbation and thumbsucking Levine & Bell [17] quote Holt's *Diseases of Infancy and Childhood* in the years 1906 to 1925 as saying In young children if masturbation is manual the hands should be tied to the side of the crib If masturbation is practised by thigh friction, the legs should be tied likewise to the corners of the crib. No one would advocate such methods now Neither is there any need to stop thumbsucking—at least until the age of six It has been shown that provided the practice stops before 6 no deformity of the teeth will result After that some 14 per cent only will show tooth deformity [8]

There are mothers who deliberately keep their infants (e g at the age of six months or so) off their feet because they think that by so doing they will prevent them

Fig. 2

developing rickets, knock knee or bow legs. I assure mothers that there is no truth in this, and that legs are made to stand and walk on.

Restriction of an older child's activity is said to be one of the causes of overactivity. Wherever possible they should be allowed to run about without restriction. It should be compulsory, as in Copenhagen, to supply adequate playing space when any block of flats is built.

Restriction of activity in children with congenital heart disease or children who have had rheumatic fever with or without carditis, is unjustified. They should be allowed to indulge in as much activity as they feel able to do. The possible exception is congenital aortic stenosis; competitive games should not be allowed.

It is difficult to advise about restrictions in the case of epilepsy. Provided that fits are under control, I feel that no restrictions should be imposed. They should, for instance, be allowed to swim under supervision.

Children with haemophilia or Christmas disease need fewer restrictions if they can be suitably protected by padding (e.g. over the knees) (Fig. 2).

Many children are kept indoors unnecessarily after an infection. I have known children kept indoors when it is several degrees warmer out of doors. This seems to me to be irrational.

Keeping Children in Bed

"The bed is often a sign of our therapeutic inadequacy rather than a therapeutic measure deserving of praise. The bed is *the* nonspecific treatment of our time, *the* great placebo." So wrote Browse [3] in his book *The Physiology and Pathology of Bed Rest*. It seems to be a totally irrational tradition in hospitals to put a child to bed as soon as he is admitted, whatever the disease from which he is suffering. When, on a ward round, I exclaimed about a girl, admitted that morning for investigation of albuminuria, having been put to bed, the ward sister said "No one told me that she should be up and about." I replied "surely the child should be up and about if well enough unless someone instructs you to confine him to bed." Not only in hospital, but in

difference to the course of an attack of diarrhoea.

With regard to diabetes, there is a legitimate difference of opinion about dietary restriction. One must do anything possible to reduce the high incidence of arterial changes after a few years, and Wilson *et al.* [20] showed how poor control of childhood diabetes is followed by a higher incidence of arteriosclerosis. Payne & Forsyth [23] however followed 100 diabetic children given a free diet and found that the incidence of arteriosclerosis was as low as or lower than that described by advocates of rigid dietary restriction.

There is no justification for giving a fat free diet for the periodic syndrome (migraine) or for urticaria. The latter is far more likely to be due to sensitivity to insect bites than to food allergy, which is a rare cause of urticaria.

Fig. 1. Swaddled baby in a Leningrad Hospital.

Physical Restriction

Swaddling of babies is still practised in some quarters. A few years ago I visited Russia and was interested to see all babies in the hospitals and coming up to the hospitals tightly swaddled. In an excellent review of the subject, Lipton Steinschneider & Richmond [18] discussed the origin of swaddling and the probable reasons for it. These included the prevention of masturbation, pacification, and an attempt to keep the legs straight. They found in experiments that swaddling does in fact reduce the amount of crying in babies. There is no evidence that swaddling does harm, though one feels some revulsion against the practice.

In the past restrictive methods were used for the treatment of masturbation and thumbsucking. Levine & Bell [17] quote Holt's *Diseases of Infancy and Childhood* in the years 1906 to 1925 as saying: 'In young children if masturbation is manual the hands should be tied to the side of the crib. If masturbation is practised by thigh friction, the legs should be tied likewise to the corners of the crib.' No one would advocate such methods now. Neither is there any need to stop thumbsucking—at least until the age of six. It has been shown that provided the practice stops before 6, no deformity of the teeth will result. After that some 14 per cent only will show tooth deformity [8].

There are mothers who deliberately keep their infants (e.g. at the age of six months or so) off their feet because they think that by so doing they will prevent them

harm at all. We have always allowed such early ambulation, and recovery has been normal.

Rheumatoid arthritis We are against immobilisation in affected children unless it is essential because of pain. Ansell & Bywaters [2], who have had extensive experience of the treatment of rheumatoid arthritis, wrote that "Every effort should be made to get the patient up walking every day even when health is otherwise reasonable. Only under rare conditions when severe constitutional manifestations, severe pain, severe hip involvement, or flexion deformities of knees and hips are aggravated by ambulation should the child be confined to bed, and then only for short periods. We have seen too much irreversible damage done by bed rest to think that it has an important part to play in the treatment of Still's disease. Muscles and bones waste joints ankylose contractures, calculi and bed sores develop, and above all, time is lost

Rheumatic fever The days of prolonged immobilisation for rheumatic fever are rapidly going At Sheffield we have for many years allowed ambulation as soon as the erythrocyte sedimentation rate has fallen to normal, which, with combined corticosteroid and salicylate treatment, usually means two or three weeks in bed, even if there is carditis [13]. There have been many studies of the effect of early ambulation since then, and all have agreed that prolonged immobilisation is useless and may be harmful. May Wilson [20] for instance who has had extensive experience of the condition, allows children up t or three weeks after instituting corticosteroid treatment. Browne [3] wrote that the one thing that lying down does not do is to rest the heart "The main reason for the use of rest in the treatment of rheumatic fever appears to stem from a fear that it might be unethical to treat it in any other way"

Infective hepatitis. After experience of treating many hundreds of cases of infective hepatitis in the Middle East, I am convinced that immobilisation is an essential part of treatment. Chalmers et al. [5] after a careful study of a mild outbreak in Korea, could find no advantage in bed rest. Others have disagreed. Capps and Barker [4], after studying 8,000 cases in the Middle East, concluded that bed rest was essential, and that activity prolonged the course of the disease and predisposed to relapses.

Poliomyelitis Dorothy Horstmann [11] showed that activity in the 48 hours after the onset of meningism increases the risk of paralysis. Ritchie Russel [25] had previously made the same observation. I feel that as long as fever persists, the child should be in bed. I would certainly keep a child in bed during the stage of meningism, hoping that the degree of paralysis, if any would be reduced.

Muscular dystrophy Dubowitz [7] described the serious harm done by putting children with muscular dystrophy to bed unnecessarily He pointed out that they undergo serious deterioration under these circumstances.

Conclusion Much harm can be done by confining children to bed when they want to be up. It bores them makes them restless and uncomfortable, makes sleep more difficult, and has a bad psychological effect. Children should not be put to bed on account of illnesses without good reason.

the private house it is a common practice to put a child to bed if he develops a cold sore throat headache abdominal discom fort, cough chickenpox or diarrhoea even though the child does not feel that he wants to go to bed. I am totally unable to understand the rationale of such a measure No one has ever explained to me why it should be expected that a child with any a sore throat or chickenpox who would like to sit in a chair reading a book or playing a game, should recover less rapidly than a child reading a book or trying to play a game when sitting in bed

A few specific conditions or groups of conditions will now be considered sepa rately

The common infectious diseases I cannot see the slightest reason why a child with chickenpox rubella, mumps or other in fectious disease if anxious to get up should not do so. I know of no evidence for instance, that bed rest accelerates the recovery from chickenpox or mumps, or reduces the incidence of complications, nor do I understand how it could do In the prodromal stage of measles many children would prefer to be in bed, but as soon as the rash emerges they would prefer to be up and about in the room I see no reason why they should not follow their inclination.

Upper respiratory tract infections If a child has a tonsillitis even with a tem perature of 100 or 101 F I see no reason why he should be confined to bed if he would prefer to sit in a chair reading or playing Gibson [9] studied the value of bed rest in a controlled study of 1 082 cases of respiratory infection, and found that there was no difference at all be- tween the two groups with regard to the duration of the illness or of fever He sug gested that children exert themselves more when in bed than when up and about. He wrote As time went by a distinct impres sion began to form that the children with a high temperature who were up and about seemed to get well just as quickly as the better-controlled children who stayed in bed

Diarrhoea. I know of no evidence that diarrhoea from any cause settles down more quickly when a child is sitting up in bed than it does when he is sitting in a chair

Tuberculosis We have had extensive experience of the treatment of primary tuberculosis and of miliary and meningeal tuberculosis, covering many hundreds of cases of each of these conditions. We have never confined children with primary tu berculosis to bed or restricted their activ ity except in the very rare case in which the child is ill. There is no need to send such a child to a sanatorium unless there are very strong social reasons in connec tion with his home As for miliary and meningeal tuberculosis, we always allowed these children to be up and about the ward as soon as they felt fit for this. The majority would be sitting up at the table in the ward to play games and eat their meals within a fortnight of admission.

Nephritis It used to be the practice to confine children with acute nephritis to bed for prolonged periods. There is no need for this Åkerren & Lindgren in Sweden [1] Joseph & Polani in England [16] and McCrory *et al* in America [19] all carried out controlled studies which showed that early ambulation, as soon as naked eye haematuria had ceased did no

harm at all. We have always allowed such early ambulation, and recovery has been normal.

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Muscular dystrophy. Dubowitz [7] described the serious harm done by putting children with muscular dystrophy to bed unnecessarily. He pointed out that they undergo serious deterioration under these circumstances.

Conclusion. Much harm can be done by confining children to bed when they want to be up. It bores them, makes them restless and uncomfortable, makes sleep more difficult, and has a bad psychological effect. Children should not be put to bed on account of illnesses without good reason.

Keeping Children Away From School

Very many children are kept away from school totally unnecessarily. At any one time about ten per cent of all school children are away from school in certain large cities in Britain. In only a small proportion of these is such absence from school justified. It seems irrational to me to keep a child away from school and yet to allow him to go to the cinema, travel in a bus and go to the Child Welfare Clinic with his brother. Unnecessary absence from school may bore the child, it worries him because he knows that he is dropping behind in work, work suffers, and it is apt to make a child a hypochondriac. In the case of asthma *it is particularly important*, for worry about school work makes him wheeze more and so he is kept off school still longer. It is a vicious circle which has to be broken.

Children are kept off school because of a cough, or a trivial wheeze, or because of a cold. They are kept off school far too long after the common infectious diseases—because of erroneous ideas of the duration of infectivity. For instance chickenpox is only infectious for 6 days after the appearance of the rash, measles till 5 days after the temperature has settled, mumps until the swelling has subsided, and rubella for 5 days after the appearance of the rash.

Quarantine

It is now widely recognised that quarantine of children exposed to infectious disease is useless, except in the case of smallpox and possibly of poliomyelitis. Smith of Rugby was one of the first to point this out [27, 24]. Others have agreed [28]. Smith reported that in 16 years' experience of 75 outbreaks of infectious disease at Rugby school there was no instance in which the originator knew how he had acquired the infection. In the same period 203 boys who had been exposed to infectious disease were allowed back to school and only one acquired the expected disease at school and there was no secondary case. If strict quarantine had been enforced, 4,224 days would have been lost. If only the susceptible boys had been quarantined, 2,123 days would have been lost. Smith remarked that family doctors go from case to case without spreading the disease.

Quarantine has not prevented the spread of disease. It is hardly to be expected that it would, for children cannot be prevented from mixing with others after school. In any case it is useless if a child has already had the infection, and cannot develop it again. Children cannot carry infectious diseases (except diphtheria, scarlet fever and poliomyelitis). They cannot be infectious in the early part of the incubation period—and it is totally irrational to keep them off school then.

There is no place for quarantine except in the case of smallpox and possible poliomyelitis.

On a par with the folly of quarantine is the refusal to permit relatives to visit their children in infectious disease hospitals. This is quite irrational and inexcusable.

Some other Restrictions in Child Management

There are mothers who will not pick the infant up when he cries in case they will spoil him. This is quite unjustified. Moth

ers who satisfy their babies' basic needs for love, food and comfort, are likely to have much happier babies than those who adopt restrictive practices in these fields.

There are mothers who overprotect their children, never letting them out of their sight, 'smothering' them instead of 'mothering' them and not letting them acquire normal independence. They dress them and feed them long after they should be able to dress and feed themselves. They worry about their child's bowels, and try to make him eat, because they fear that he will not eat enough unless he is forced, cajoled and coaxed to eat. They do not realise that the only cause of a poor appetite in a well child is food forcing on the part of the parents.

Every child has to experience stress. A good example of the psychological effect of complete protection from stress in childhood is the story of John Ruskin. We have described this and other examples of over protection, in a book about the childhood of 450 famous men and women [15].

Overprotection leads to excessive dependence of the child on the mother to insecurity and accident proneness. In the same way excessive strictness and excessive discipline lead to rebellion, insecurity and again to accident proneness. Children must be allowed to develop independence and a sense of responsibility to experiment and to learn.

Conclusion

All children need to learn discipline. Some restrictions are necessary for all children. But there are many undesirable restrictive practices which do harm. These have been summarised.

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Some Shortcomings of Medical Education in a Free Society

by CHARLES A. JANEWAY

It is an honor to contribute to this *volume in memory of Professor* Constantin Choremis, with whom our clinic had close ties through several of his pupils who came to Boston for part of their training and enriched the life of our medical institutions. Moreover a few years ago I had the privilege of visiting Athens and of being shown by Professor Choremis and his students, not only the pediatric problems with which they were struggling, but also some of the glorious expressions of the creative spirit which made ancient Athens the source of so many of the cultural values at the heart of western civilization. It is because Professor Choremis was not only a distinguished pediatric physician and teacher but a humanist as well, that I have chosen in this essay in his honor to examine some of the shortcomings of medical education in meeting the needs of a free society in my own comparatively young country

We live in a world in which good health services and medical care are now considered the right of every citizen. No longer is disease endured fatalistically nor is access to good medical care accepted as the sole prerogative of the wealthy. This deep-seated change in attitude on the part of the masses of people under every type of government all over the world is the product of two of the great revolutions of modern times. The first is the *scientific revolution*, which has changed medicine from a largely empirical system for palliating symptoms to a highly *effective* applied scientific discipline capable of preventing or curing many formerly inescapable diseases. The second is the *social revolution*, which has stirred the hitherto torpid masses of humanity to what has been called "the revolution of rising expectations

Thus, armed with an increasing capability of conquering disease and prodded by the demands of the people for better health and medical care, the health professions must not only provide but distribute trained personnel so as to achieve maximum efficiency in applying modern scientific knowledge to the betterment of health and the alleviation of suffering. This requirement for trained manpower is the responsibility of the educational system which must recruit and produce the necessary personnel to meet society's needs. Unfortunately in the case of medicine, the time required to train competent phy

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sirable in clinical departments. However the full-time system, with its emphasis upon research has become almost universal in the United States, and has been a major force in promoting the increasing specialization which characterizes American medical practice.

This trend toward specialization has also been fostered by increasingly rapid advances in the medical sciences, which have been responsible for the extraordinary progress in curative medicine and surgery during the past 50 years. This expansion of medical knowledge and of the skills required for its application have lengthened the period of hospital training for future physicians and have forced people into specialization, in order that they may feel competent and comfortable within a finite body of knowledge which they can comprehend. Furthermore the change from empirical to scientific medicine has made the teaching hospital the focus of clinical teaching, rather than the patient's home where the apprentice used to learn medicine at the bedside from his physician master in nineteenth century America. In the teaching hospital, with its laboratories, X-ray department, and well-equipped operating rooms, the student sees modern medicine and surgery being practiced by highly competent specialists He sees acute episodes of serious disease being treated ith spectacular success, but he has little contact with the problems of diagnosis in the home or busy office, with the daily care of patients with the minor illnesses and functional disturbances which make up the bulk of morbidity among the populace, or with the skills required to provide long-term care for the patient confined to his home or handicapped by a serious chronic disease. Nowhere in his career as a medical student or as an intern or resident does he have appreciable contact with teachers concerned with family medical care No wonder that he inevitably gravitates into a specialty or that general practice attracts fewer and fewer graduates from our medical schools.

Meanwhile, socio-economic changes have exerted a tremendous influence upon medical practice. The increasing prosperity of our population, as a result of the diffusion of wealth, education and earning power through an increasingly wide segment of our society has meant better housing, better nutrition, and better health practices in the home, all of which have had a subtle effect in steadily lowering the mortality from infectious diseases quite independently of advances in preventive and curative medicine There has been a marked shift in the pattern of American family life accompanying the transition from what was primarily a rural, small town society to an urban suburban culture brought about by increased agricultural productivity rapid industrialization and the mobility made possible by the automobile This shift has broken up the large multi-generation household of former days and moved the majority of our people into small, single-family suburban houses where parents live crowded in with their two or three children, often far away from other relatives. The grandmothers and maiden aunts who used to play such an important supportive role in bringing up children are no longer available, and the young mother turns to her pediatrician for answers to many questions about childbearing and child development that would never have

sicians is probably longer than for any other profession, no cadre of previously trained reserves is available to meet unexpected demands. Therefore it is extremely difficult to expand health and medical services as rapidly as they are being demanded in today's world

Adjustment of the educational system to meet present and anticipated needs for trained manpower is far simpler in a totalitarian than in an open society such as we enjoy in the United States or in western Europe The system followed in most countries with political freedom has been a "laissez faire" one, in which it has been assumed that financial and other inducements, such as the desire to serve and the desire for prestige would tend to draw manpower into those professions and occupations where the need and hence the demand was greatest. The main difficulty with this system is that needs are now changing so rapidly that the period of at least nine years, which must elapse between an individual's decision to enter the medical profession and his emergence as a trained physician, is far too long for satisfactory adjustment between supply and demand to take place Thus grudgingly our country is being forced to adopt some degree of long range educational planning although it is pluralistic and far less rigid and monolithic than the planning of most totalitarian countries or of those democratic nations where educational policies and the funds for their implementation are practically all under the control of a central Ministry of Education.

It is instructive to examine what has happened to the supply of physicians in our country as a result of the successful efforts by the medical profession to im prove the quality of medical educatio the impact of advances in medical scienc and the socio-economic developments o recent years

In the early twentieth century whe progress in the medical sciences began t make modern scientific medicine possible deficiencies in the scientific education o many of our physicians became increasingly apparent This led the medical profession to examine our system of medical education an examination which culminated in the Flexner report in 1910 This report prepared by a distinguished schol and educator who was not himself a ph sician led to far reaching reforms in mo American medical schools and to the el mination of a large number of medic schools of poor quality The two princip results of the Flexner report were first drastic reduction in the number of place open to those who desired to embark upo a medical career second introduction o the full time system[1] into clinical depart ments The latter step which greatly improved the scientific basis of clinical teaching initiated the great emphasis upon research rather than mere clinical skill, as the criterion for academic advancement which has characterized modern American medical education. This has had far reaching consequences, and it is interesting that one of the major proponents of this system, who accepted the first full time professorship of medicine in the United States in 1914 by 1917 had already come to the conclusion that it was not necessarily de-

[1] The full time system means that the clinical teacher devotes all his time to teaching and research, does not practice for himself and derives his financial support wholly from his academic and hospital salary

where doctors are adequate in numbers, rapid scientific and social changes have rendered their training which is excellent preparation for physicians for the crowded urban areas or the developing countries, unsuitable to enable them to cope in a professional manner with the multitude of minor illnesses, functional disturbances and family stress situations which turn out to be such frequent problems in suburban practice.

We have shown how medical education has failed to produce the number of doctors needed or demanded by our society today and that the available doctors are neither equitably distributed nor properly trained for the demands of modern practice. All of these deficiencies may be explained on the basis that the rate of change—both in medicine and in our society—has outstripped the capacity of our educational system to adapt to it. University medical schools have been so engrossed in the extraordinary successes of the medical sciences in overcoming the life-threatening and crippling diseases which are concentrated in our teaching hospitals that they ha failed to pay adequate attention to the overall health needs of the community or to examine scientifically the ways in which medical knowledge can most effectively be pplied to improve the health of our people. Fortunately this is changing. Medical care is becoming the subject of intensive investigation in a number of medical schools; furthermore the provision of comprehensive care to urban poor families is now being undertaken, with government support, by medical schools and hospitals in our larger cities. With research tools derived from the behavioral sciences—cultural anthropology sociology psychology statistics—it should be possible to study medical practice and to experiment with it at a family level, so as to achieve more *effective* ways of applying our enormously potent biological knowledge to the improvement of health.

In this essay specialization has been mentioned frequently as an inevitable consequence of scientific advances, but as an evil in that it has increasingly deprived our society of the general practitioners which it needs. Since scientific progress is bound to continue, it seems inevitable that specialization in medicine will continue to increase rather than diminish. Who then is going to meet the health needs of families, who is going to provide primary medical care in this day when most doctors, already in short supply are becoming specialists?

Several possibilities suggest themselves to meet the needs of families for comprehensive health and medical care. The first is *group practice*, whereby doctors representing a number of specialities work together in providing medical care in a given community. This method of practice has proven to have many advantages in private medical practice in the United States, has become widespread and will almost certainly continue.

A second possibility which is not incompatible with the first, but which would further strengthen it is the creation of a new specialty *family medicine*. General practice is no longer possible because the great advances in medicine and surgery are too much for one man to learn or use well. It has the added disadvantage that

been put to a physician forty years ago Unfortunately the pediatrician magnificently trained to recognize and to treat severe life threatening disease through his hospital experience as an intern and resident, has not had the basic education in psychology to equip him to deal scientifically with the problems of behavior and learning which prove to be far more frequent and troublesome in his practice than the meningitis, diabetic acidosis, diarrhoeal dehydration or cardiac failure with which he became so familiar during his hospital years. Thus, the expectations and demands of the public with regard to medical care have broadened in scope and increased in amount faster than medical education has been able to adapt to these new needs.

While the bulk of our population has been involved in what amounts to an enormous shift into middle-class living in the suburbs, the 20–30% of our people who are poor many of them Negroes who have been displaced from farm labor in the southern United States, have gotten poorer and have become concentrated in the slum areas of our great cities. Here because of limited education during their rural childhood the parents have difficulty in obtaining any but the most menial unskilled jobs. Poorly paid often unemployed, ignorant of good health practices, crowded into the worst housing their maternal infant and tuberculosis mortality rates are much higher than average and the high incidence of family problems and social pathology further contributes to their miseries. Doctors entering practice settle in the suburbs where their patients can pay where living is pleasant and where the educational opportunities are best for their children. Consequent the poor in the cities, where good medi care is most needed, have fewer and few doctors available to them. Fortunatel free preventive services are provided the municipal departments of health wh the clinics of the great urban hospit provide treatment to all for acute illness but this gives a fragmented type of fam health care, rather than the comprehe sive care combining preventive and cu tive medicine which the family pediat cian offers to his wealthy well nourishe suburban families.

Thus on the one hand the scienti advances which have strengthened me cal education have limited the number doctors being trained, but increased th sophistication and skill in treating a preventing life-threatening diseases, whi on the other hand, the rapid rise in nu bers, in prosperity and in understanding health of the majority of our people ha enormously increased the demand for me ical services for those who can pay a the need for it among those who canno Because modern medicine is effective has become much more essential than t empirical medicine of the last centur Therefore we have a *quantitative* shorta of physicians because public expectatio have exceeded the rate at which they ha been produced.

But we also have a *qualitative* proble because even the doctors we have are n distributed in relation to the need f medical care since they are concentrate in the suburbs where health standards a highest and relatively few are in the gre urban centers where poverty overcrow ing and ignorance have created the grea est need. Finally even in the suburb

new knowledge through research, but to take responsibility for the study of the application of knowledge for the benefit of society even if it means considerable involvement in the life of the community. I believe this is a point of view that would have found favor with Socrates and his school.

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it has less prestige, is more poorly rewarded than a specialty and thus tends to attract those with the poorest training. However, it is my belief that a group of physicians, trained properly to provide health and medical services to all members of a family or household, would fill a tremendous void in medical services in our country. These physicians should be specialists in people rather than in diseases. Their training should be as rigorous as for any other specialty. It should include pediatrics, internal medicine, psychiatry, epidemiology and preventive medicine. Their role would encompass diagnosis with their principal responsibility the determination of whether or not an illness was sufficiently serious to require referral to a specialist; treatment of acute minor illnesses and of chronic illness in conjunction with a specialist, preventive medical practices (immunization, nutrition, cancer detection, health education) and the handling of the multitude of anxieties, emotional disturbances and problems of adjustment which occur in families. One may ask how society can afford to have specialists in charge of the health of families. The answer, I believe, is twofold: first, they should be able to minimize serious illness, much of which is preventable; second, we must learn how to make more efficient use of all doctors, whose professional training requires so much time.

Consequently, a third possibility is to increase *the use of ancillary personnel in medical practice.* The nurse-midwife, the public health nurse, the social worker, the clinical psychologist, all of them skilled, but less trained than the physician, can, by working as a team under his direction multiply many fold the number of families he can care for competently.

Thus one might visualize medical and health services being provided in a community by a group practice of specialists, providing diagnostic and therapeutic services for specific diseases at a central hospital, closely allied with a group of specialists in family medicine, each of whom, assisted by a team of health workers, provides primary medical care to a large group of families. Such a scheme would combine the advantages of each of the three possibilities enumerated—group practice, family medicine and the use of ancillary personnel. This is obviously an idealized scheme and perhaps impractical. What is needed is research and experimentation in medical care conducted with as rigorous scientific standards as have been applied to biological research in the laboratory, so as to provide the knowledge which will permit medical practice to evolve in a way that will most effectively meet the health needs of the people in their particular culture.

Another essential responsibility of medical education, in this day of rapid scientific progress and constant change, is the continuing education of all physicians in practice. With much of his education becoming obsolete within a few years after completion of medical school and hospital training, the practicing physician must have the opportunity to study recent advances in his field at periodic intervals.

These are some of the challenges which face medical education in our country at this time. I believe it is the task of a university not only to preserve and hand on knowledge from the past and to provide

bator enables us to remo e protective clothing and thus makes possible better observation of the infant in the first critical days of life. Modern incubators moreover have devices for increasing the percentage of oxygen in the gas mixture the child is breathing. The introduction of modern incubators has surely improved the prognosis of the newborn infant with a low birth weight. However these apparatuses have some disadvantages. Careful investigations and catheterization of the umbilical arteries or vein, for instance are difficult to perform. Moreover the child may lose energy in an incubator by infra-red radiation. This is especially the case when the incubator is placed in a room with relatively cold walls and windows. Infections of incubators, especially of humidizing systems, with drug resistant micro-organisms (pseudomonas aeruginosa) have been reported from different hospitals. Modern incubators with an electric heating system are difficult to sterilize.

In the University Hospital of Groningen we try to avoid these difficulties by keeping infants with a low birth weight in a room with a constant temperature of 32° This temperature is only one or two degrees lower than the neutral temperature of most infants born with a low birth weight. A napkin is, in most cases, enough cover to keep the body temperature constant and the metabolic rate near that at the neutral temperature of the child. Care should be taken to avoid heat losses by infra red radiation, since greater parts of the infants skin are not covered at all. In our nursery an electric heating system in the ceiling keeps the temperature of the ceiling and part of the walls at about 40°C thereby preventing heat losses by infra red radiation. This electric heating system is used to keep the room temperature constant. *Most of the heat, however* is supplied by a usual central heating system. Air is blown into the room from outside and is electrically heated as it enters the room. Because the air in our town is not heavily poluted, we have no special system for cleaning the air nor do we have a complicated system to regulate the humidity The Dutch climate being humid, it is sufficient to mop the floor of the nursery twice a day to keep the relative humidity in the room at about 60 %. A higher degree of humidity is not likely to have great advantages, mainly because in many cases we give early intravenous fluids to the child, thus *compensating for water losses by respiration.* On the contrary a constantly high degree of humidity increases the risk of abundant growth of micro-organisms. Moreover a higher degree of humidity at this temperature makes work in the rooms for doctors and nurses difficult. With a relative humidity between 50 % and 60 % the heat in the premature unit is not felt to be oppressive by those working there provided there are facilities for taking a shower and changing clothes. With our system the possibilities for observation and investigation are better and the number of infections has decreased after the new system has been introduced. An additional advantage is that the nursing work in such a unit is less time-consuming. We now have two units in which 12 prematures are treated. The total number of nurses necessary is on the average 6.5 Each nurse works 40 hours a week. Therefore, at daytime two nurses and at night one are available for 12 infants

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From the Department of Pediatrics, University of Groningen. Head: Professor J. H. P. Jonxis

A Premature's Nursery without Incubators

by J. H. P. JONXIS

Compared with the adult, the newborn has a large body surface. This, together with the thinness of his skin and subcutaneous fat layer, is why his heat loss is considerably greater per kg of body weight than that of the adult. To keep his body temperature constant, his metabolic rate has to increase much faster than that of the adult as soon as the environmental temperature falls below the neutral temperature. The newborn at term and even the premature responds to a colder surrounding by a rise in oxygen consumption. This rise is, however, compared with that which occurs in the older individual, not large enough to compensate for the heat losses. Even a relatively small drop in the environmental temperature soon causes a drop in the body temperature although there is an initial rise in oxygen consumption. At first, only the temperature in the outer layers of the body drops. The temperature of the central parts of the body are kept as long as possible within the normal range. In a primitive society in which no possibilities exist in the form of clothes or fire to keep the child warm, heat produced by the human body is the only way of preventing a drop in temperature of the newborn. The first primitive beings, in the time before the invention of body protection against cold with hides or leaves and before fire came into use, must have lived in a tropical country in which even at night the temperature did not drop regularly below 30°C; otherwise the newborn would not have survived. Today clothes and heating are available to prevent larger heat losses in the newborn child and life in primitive groups is possible even under arctic conditions (Eskimos).

Special care is needed, however, to keep the body temperature of infants with a low birth weight constant. The body surface of these infants is per kg body weight still larger than that of the child born at term. Moreover, their metabolic response to cold is less pronounced than that of an infant with a normal birth weight. The neutral temperature, that is the temperature at which the metabolism is lowest, is in these infants a few degrees higher than that in the infant born at term. Protection against cooling with clothes and eventually hot water bottles is usually not sufficient to keep their body temperature constant. Therefore, such children are placed in boxes or incubators in which the temperature is kept constant at a level close to the neutral temperature of the child. This high environmental temperature in the incu-

bator enables us to remove protective clothing and thus makes possible better observation of the infant in the first critical days of life. Modern incubators moreover have devices for increasing the percentage of oxygen in the gas mixture the child is breathing. The introduction of modern incubators has surely improved the prognosis of the newborn infant with a low birth weight. However these apparatuses have some disadvantages. Careful investigations and catheterization of the umbilical arteries or vein, for instance are difficult to perform. Moreover the child may lose energy in an incubator by infra-red radiation. This is especially the case when the incubator is placed in a room with relatively cold walls and windows. Infections of incubators, especially of humidifying systems, with drug resistant micro-organisms (pseudomonas aeruginosa) have been reported from different hospitals. Modern incubators with an electric heating system are difficult to sterilize.

In the University Hospital of Groningen we try to avoid these difficulties by keeping infants with a low birth weight in a room with a constant temperature of 32° This temperature is only one or two degrees lower than the neutral temperature of most infants born with a low birth weight. A napkin is, in most cases, enough cover to keep the body temperature constant and the metabolic rate near that at the neutral temperature of the child. Care should be taken to avoid heat losses by infra red radiation, since greater parts of the infants skin are not covered at all. In our nursery an electric heating system in the ceiling keeps the temperature of the ceiling and part of the walls at about 40°C, thereby preventing heat losses by infrared radiation. This electric heating system is used to keep the room temperature constant. Most of the heat, however is supplied by a usual central heating system. Air is blown into the room from outside and is electrically heated as it enters the room. Because the air in our town is not heavily poluted, we have no special system for cleaning the air nor do we have a complicated system to regulate the humidity. The Dutch climate being humid, it is sufficient to mop the floor of the nursery twice a day to keep the relative humidity in the room at about 60 %. A higher degree of humidity is not likely to have great advantages, mainly because in many cases we give early intravenous fluids to the child, thus compensating for water losses by respiration. On the contrary a constantly high degree of humidity increases the risk of abundant growth of micro-organisms. Moreover a higher degree of humidity at this temperature makes work in the rooms for doctors and nurses difficult. With a relative humidity between 50 % and 60 % the heat in the premature unit is not felt to be oppressive by those working there provided there are facilities for taking a shower and changing clothes. With our system the possibilities for observation and investigation are better and the number of infections has decreased after the new system has been introduced. An additional advantage is that the nursing work in such a unit is less time-consuming. We now have two units in which 12 prematures are treated. The total number of nurses necessary is on the average 6.5 Each nurse works 40 hours a week. Therefore, at daytime two nurses and at night one are available for 12 infants.

Perhaps it is worth mentioning a few additional points When extra oxygen is needed by infants with a low arterial oxygen saturation a small oxygen tent is used. A very small premature may need a higher environmental temperature than our room temperature (32°C) to keep his body temperature constant By placing a perspex bell over the child the temperature in the bell rises about two degrees over the room temperature This is caused by heat production in the child and infra-red radiation from the electric heating system in the ceiling In a few exceptional cases a special perspex bell is used in which the temperature is kept constant by circulating water with the required temperature. When perspex bells are used, air eventually oxygen, is blown inside at a speed of 1 l per minute. For better observation and treatment the doctor and nurse should have free access to the child. To achieve this the incubator should have the size of a room

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From the Pediatric Clinic of Athens University

Glucose 6 Phosphate Dehydrogenase Deficiency in Female Heterozygotes and the X Inactivation Hypothesis

by CHRISTOS A. KATTAMIS

During the last decade an enormous literature about the many aspects of G-6-PD deficiency has been published [4, 17]. It was recognised from the very beginning that heterozygotes for G-6-PD deficiency may have normal, intermediate or very low levels of enzyme activity. Originally in a study of 6 mothers known to be heterozygotes by pedigree analysis, Childs et al [7] found 4 normal, 1 intermediate and 1 grossly deficient, in respect to GSH instability. Similarly Sansone [22] reported that of 10 heterozygote mothers of deficient males, 3 were normal, 4 intermediate and 3 deficient. Our own results with the GSH stability test in 44 mothers of male patients with favism revealed 10 normal, 30 intermediate and 4 deficient [26]. Quantitative G-6-PD determinations in 89 mothers of deficient males disclosed that levels of activity were normal in 13, grossly deficient in 10 and intermediate in 66 [12]. In these studies homozygote females had not been excluded by complete genetic studies.

For a long time the wide variation in enzyme activity in heterozygotes remained unexplained. Recently however the X inactivation hypothesis advanced by Lyon [16] offered an explanation for these findings which in turn are strong evidence that X inactivation does occur in the human female.

In the present communication data are presented on G-6-PD activity in heterozygotes detected by pedigree analysis and investigated by a combination of laboratory methods. An interesting pedigree is reported, in which enzyme activity is characteristic of the variations encountered in heterozygote females. This family was detected during the investigation of 68 other families. Finally these observations are discussed in relation to Lyon's hypothesis.

Material and Methods

76 female heterozygotes detected by careful pedigree analyses of G-6-PD deficient families were studied. A female was considered to be a true heterozygote if

(i) She was the mother of a deficient male and had either a normal son or a normal father.
(ii) She was the daughter of a deficient father and had either a son or a mother and brothers who were normal.
(iii) She was born to a homozygote mother and a normal father.

Thus all females homozygotes were excluded.

G-6-PD activity was investigated by the

TABLE 1 *Standards of our laboratory for the methods employed in the study*

Methods	Range		
	Normal	Intermediat	Grossly deficient
B.C.B. decolorization (time in min)	30–60	60–150	> 150
G-6-PD activity (units per 100 ml/PRC)	180–520 (394 ± 61)	40–280	0–40
Methemoglobin reduction (screening test)	0	0–+ + +	+ + + +
Cyanmethemoglobin elution technique (percentage of normal cell)	95–100	6–95	0–5

B.C.B. = brilliant cresyl blue. PRC = packed red cells)

brilliant-cresyl blue (B.C.B.) decolorization test [12, 18] the quantitative measurement of G-6-PD activity [8, 1., 27], the combined methemoglobin reduction test (screening test) [5] and the cyanmethemoglobin elution technique [15]

By the last method two distinct red cell populations can be identified in most heterozygotes, one consisting of stained cells with normal activity (Fig 3a) and another consisting of unstained cell ghosts with grossly deficient activity (Fig 3b)

Table 1 summarizes standards of the four methods in our laboratory Normal values for G 6-PD activity have been obtained from 100 normal males [12].

Results

Female heterozygotes

The results of G-6-PD activity in heterozygotes have been summarized in Table 2 Figure 1 illustrates G 6-PD activity in all heterozygotes studied. It can be seen that it ranged from 0–520 units/100 ml of packed red cells i.e. from total absence to normal Fifty two (69.3 %) had intermediate values, ranging between those of grossly deficient males (< 10 % of the normal mean) and those of low normal (> 80 % of the normal mean); five (7 %) had very low and 18 (24 %) had normal activities It is of particular interest that of 18 heterozygotes with normal activity 13 had very low normal levels, and in only 5 was the activity at or above the normal mean Thus heterozygotes with rather high normal activity were *very few* and so were those with complete enzyme *deficiency*

The cyanmethemoglobin elution technique proved very helpful in differentiating the two red cell populations in heterozygotes with intermediate G 6-PD values. *On the contrary* we found it very difficult or even impossible to predict heterozygotes with normal enzyme activity The validity of this method and the discrepancies observed have been already discussed by others [6 21]

Pedigree analysis

The results of the biochemical investigation of all members of the *G-6-PD* deficient family are clearly illustrated in Fig 2. Numbers indicate units of *G-6-PD* activity per 100 ml of packed red cells and numbers in parenthesis the percentage of deficient cells by the cyanmethemoglobin elution technique

In this family the deficient grandfather (I_1) gave birth to 3 daughters who were expected to be heterozygotes. However

TABLE 2. *G-6-PD activity in 75 heterozygote females tested by four methods*

Methods	Total No. cases	Normal N	Normal %	Intermediate No.	Intermediate %	Grossly deficient No.	Grossly deficient %
B.C.B. decolorisation	75	39	51.9	26	34.5	10	13.3
Methaemoglobin reduction (screening test)	75	19	25.3	48	63.6	8	10.7
Cyanmethaemoglobin elution technique	5	25	33.3	43	57.3	7	9.3
Quantitative G-6-PD determination	75	18	24.0	52	69.3	5	7.0

biochemical investigation revealed that G-6-PD activity in the first daughter (II_2) was within the normal range (388 units/100 ml) with 100% stained erythrocytes (Fig. 3a); the second daughter (II_3) was totally deficient with 100% unstained erythrocytes, and the third (II_4) had intermediate levels of activity (208 units/100 ml) and 70% of unstained erythrocytes.

The same variation in G-6-PD activity was observed in the third generation. II_4 who was completely deficient gave birth to 3 heterozygote girls in whom G-6-PD activity was respectively 0, 120, and 230 units/100 ml of packed red cells.

Pedigree analysis also shows that II_4 and III_5 were not homozygotes since the first had two normal sons, and the second a normal father.

This pedigree illustrates very clearly the wide range of G-6-PD activity in female heterozygotes, derived from the same ancestor.

Discussion

In 1960 Ohno & Hauschka [20] demonstrated that the two X chromosomes in females of various mammalians were different, one resembling the autosomes, the

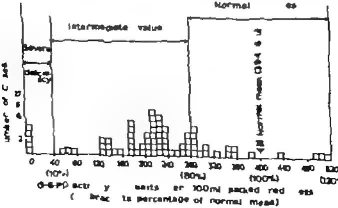

Fig. 1. G-6-PD activity in 75 female heterozygotes detected by pedigree analysis.

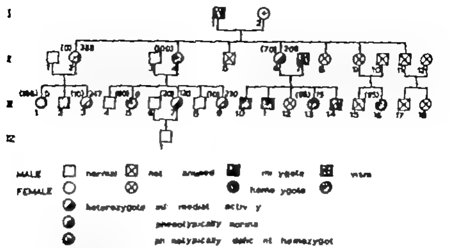

Fig 2. Pedigree illustrating the wide variations of G-6-PD activity in heterozygote females. Arabic numbers over females indicate enzyme units per 100 ml of packed red cells, and numbers in parenthesis the percentage of unstained (deficient) cells.

other being hyperpyknotic and forming the sex-chromatin body. This observation led Lyon [16] to suggest that the hyperpyknotic X-chromosome is genetically inactive that inactivation takes place early in embryonic development and that the progeny of each cell show the same pattern of inactivation.

At present the evidence that one of the X chromosomes is inactivated in the normal human female is incomplete although for some loci of the X-chromosome the evidence is very strong [25]. Accumulating data on G 6-PD deficiency confirm, directly or indirectly that the theory of X inactivation may be nicely applied to the sex linked locus of glucose-6-phosphate dehydrogenase. This locus has already been used as a genetic marker in studies on X chromosome inactivation in the normal human female [1 2].

Originally it was demonstrated that the methemoglobin reduction rate and the reduced glutathion stability test in erythrocytes from females heterozygous for G 6-PD deficiency followed a two com

Fig. 3. Results of the cyanmethemoglobin elution technique in three heterozygotes of the pedigree (a) stained cells with normal enzymic activity II_2. (b) Unstained (ghost) cells with total absence of activity II (c) Two populations of normal and deficient cells in heterozygote with intermediate levels of activity II_4

ponent curve closely resembling that obtained from mixtures of normal and deficient cells [2]. Later G-6-PD deficient erythrocytes were separated from the normal cells in a female heterozygous both for G-6-PD deficiency and sickle-cell anemia, the enzymic activity of the deficient cells was shown to be very similar to that of G-6-PD deficient male. These findings were suggestive of the presence of two red cell populations [3].

Red cell mosaicism in the female heterozygote was also confirmed, rather directly by other methods. In most heterozygotes two red cell populations can be demonstrated by the quantitative cyanmethemoglobin elution technique, one with normal, the other with grossly deficient activity [23, 24]. Decreased enzymic activity with evidence of cell mosaicism has also been observed in skin cultures from heterozygotes [10]. Cloning in these cultures from heterozygotes has confirmed beyond any doubt the presence of two types of cells, i.e., clones with normal and clones with low enzyme activity [9]. Till now no serious evidence has been presented against cell mosaicism in female heterozygous for G-6-PD deficiency [4]. In the light of these observations an explanation for the greatly varying expression of G-6-PD activity in heterozygotes is no longer impossible. It has been shown in the present investigation that in heterozygotes detected by detailed pedigree analysis excluding all probable homozygotes, enzyme activity ranged from complete absence to entirely normal levels. In 7.0% there was complete absence or very low activity corresponding to that of deficient males or homozygotes with the Caucasian type of the deficiency usually encountered in Greece [8, 11, 12, 19]. In 89.3% values were intermediate and in 4% normal.

In this investigation it has also been confirmed by the cyanmethemoglobin elution technique that most females with intermediate levels of G-6-PD activity had two red cell populations, one normal, the other resembling that of deficient males. With very few exceptions the percentage of each of cell population was proportional to the level of enzyme activity. A uniformly normal cell population was found in heterozygotes with normal enzyme activity and a uniformly deficient population in grossly deficient heterozygotes. The presence of very few (<5%) deficient cells in the former or normal cells in the latter does not, in our opinion, indicate heterozygosity. These findings also show that heterozygotes cannot all be detected by the laboratory methods available.

Complete pedigree analysis may prove to help considerably in determining the genotype of a female heterozygote [13, 14]. The pedigree reported in this study appears to be unique in that it demonstrates great variations in the expression of G-6-PD activity in heterozygotes belonging to the same family. Intermediate levels in heterozygotes are to be expected as a result of the dosage effect of the mutant gene. What was really puzzling was the considerable proportion of heterozygotes with either normal or extremely low enzyme activity.

These findings indicate that enzyme activity in heterozygotes depends upon the ratio of normal to deficient red cells. This ratio is probably related to the proportion of progenitor cells in which a

normal or a deficient X chromosome has been inactivated. The X chromosome appears to be inactivated at a very early stage of development when only a very small number of cells, perhaps 3 or 4 serve as progenitors [2, 16]. The inactivated X-chromosome is replicated with every cellular division but remains inactive during interphase. It follows then that in a female heterozygote the normal allele will be expressed in some body cells and the deficient allele in others. Variations in enzyme activity of the female may be explained by the very fact that the X-chromosome is inactivated in a limited number of progenitor cells; considering that X inactivation is random in some heterozygotes the precursors of the erythroid series may be all expected to contain by chance the X chromosome bearing the inactivated normal gene. The entire erythroid series would consist of cells with the mutant gene for G-6-PD activity and heterozygotes would be completely deficient with only one population of deficient cells. Similarly heterozygotes with normal G-6-PD activity may result from inactivation of the X-chromosome bearing the mutant gene in all progenitor cells. In heterozygotes with intermediate levels of activity and two red cell populations inactivation may have occurred of the normal X-chromosome in some progenitor cells and of the mutant X-chromosome in others. A mosaic with two cell populations would be thus produced. G-6-PD activity in these cases would depend upon the ratio of inactivated normal to mutant X-chromosomes; and since inactivation is merely a matter of chance it is evident that in the majority of heterozygotes values of G-6-PD activity will be intermediate and that there will be a wide individual variation in the intermediate values.

Summary

The levels of G-6-PD activity in all female heterozygotes detected by pedigree analysis are reported together with biochemical and genetic data of a pedigree in which a wide variation in G-6-PD activity was revealed in heterozygotes. The results strongly favour the hypothesis that one X chromosome is inactivated during early embryonic development in the human female at least as far as the locus of G-6-PD is concerned.

Acknowledgements

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normal or a *deficient* X-chromosome has been inactivated. The X chromosome appears to be inactivated at a very early stage of development when only a very small number of cells, perhaps 3 or 4 serve as progenitors [2, 10]. The inactivated X chromosome is replicated with every cellular division but remains inactive during interphase. It follows then that in a female heterozygote the *normal* allele will be expressed in some body cells and the deficient allele in others. Variations in enzyme activity of the female may be explained by the very fact that the X chromosome is inactivated in a limited number of progenitor cells; considering that X inactivation is random in some heterozygotes the precursors of the erythroid series may be all expected to contain by chance the X chromosome bearing the inactivated normal gene. The entire erythroid series would consist of cells with the mutant gene for G-6-PD activity and heterozygotes would be completely deficient with only one population of deficient cells. Similarly heterozygotes with normal G-6-PD activity may result from inactivation of the X chromosome bearing the mutant gene in all progenitor cells. In heterozygotes with intermediate levels of activity and two red cell populations inactivation may have occurred of the normal X chromosome in some progenitor cells and of the mutant X-chromosome in others. A mosaic with two cell populations would be thus produced. G-6-PD activity in these cases would depend upon the ratio of inactivated normal to mutant X-chromosomes, and since inactivation is merely a matter of chance, it is evident that in the majority of heterozygotes values of G-6-PD activity will intermediate and that there will be a wi individual variation in the intermedia values.

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mg/100 ml, 4.7 mg free 6.5 mg conjugated. Serum alkaline phosphatase was 25.0 King Armstrong units/100 ml; flocculation tests were negative. The serum G O T was 55 K units/ml and the G.P T 25 K units/ml. Urine was strongly positive for bile, but was free from protein. The total urinary catecholamines were *80 μg/100 ml* (1.2 μgm/mg of creatinine) and the V.M.A. was 244 μgm/100 ml (5.4 μgm/mg of creatinine), both these figures being within normal limits. Lumbar puncture produced yellow fluid under normal pressure. Queckenstedt's test was negative. The fluid contained 400 mg of protein/100 ml with a positive globulin test. C.S.F sugar was 72 mg/100 ml. Very few cells were present. Chest and skeletal X-ray showed no abnormality and abdominal lymphangiography showed that the glands which were opacified were of normal size and architecture. However examination under anaesthesia whilst the lymphangiogram was being performed revealed a number of very large glands and these did not fill at all with the radio-opaque medium. Biopsy of a cervical lymph node showed a proliferating mass of lymphocytes with invasion of the capsule and surrounding tissues and many mitotic figures.

The diagnosis was therefore generalised lymphosarcoma with obstructive jaundice probably due to gland pressure at the porta hepatis; compression paraplegia due to lymphosarcomatous involvement of the lepto-meninges.

Despite the widespread disease it was thought that the patient's general condition was good enough to justify a trial of chemotherapy in the hope of producing some palliation. He was started on treatment with Vincristine the first dose being 0.05 mg/kg intravenously and Prednisolone 10 mg 3 times daily. Further doses of Vincristine were given at weekly intervals, the increment being 0.025 mg/kg for each dose. In the next two weeks the jaundice decreased, the serum bilirubin falling to 5 mg/100 ml, and he began to have slight movements *of his legs*. One month after starting treatment he developed a swelling on the anterior aspect of the tibia and X-ray showed marked destructive changes at this area. At this time, jaundice was very much less and there was considerable increase of the amount of voluntary movement in the lower limbs.

Six injections of Vincristine at weekly intervals were given after which he was started on Cyclophosphamide 30 mg daily by mouth; Prednisolone was gradually reduced. *He then developed a firm swelling of* the left mandible which rapidly increased, involved the gums and produced loosening of a number of teeth. Although there had been further improvement in muscular power of the lower limbs, he was still unable to stand and there was no subsequent improvement. Over the next few weeks he developed further neurological signs including proptosis of the right eye, left facial paralysis and bilateral sixth nerve paralysis. Rapid growth of tumour on the other side of the mandible made it difficult for him to eat, although he was still quite conscious and cheerful. Local radiotherapy to the jaw produced some improvement. Despite all these complications he was able to be discharged home after 2½ months in hospital and he had a comfortable month at home before his final admission in coma and his death shortly afterwards.

At post mortem examination the main findings were the deposits in the mandible an enlarged lymph node below the left kidney and a few sites of previous disease in lymph nodes represented by shrunken yellowish-brown areas. Deposits were present in the dura and there was diffuse thickening of the lepto-meninges over the base of the brain, extending along the cranial nerves and of the spinal cord meninges with the emerging nerves.

2. *Lymphosarcoma*

R. J was 18 months old when he was first admitted to hospital. He had been ill at home for a month with obstructive jaundice and during the 2 weeks before admission he had had occasional haematemesis and melaena.

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From the Alder Hey Children's Hospital, Liverpool Head S E Keidan, Consultant Paediatrician

Paraplegia in Childhood Malignant Disease

by †S. E. KEIDAN

It is a great honour to be asked to collaborate in paying tribute to the memory of Professor Choremis whose sudden death was so great a loss to Paediatrics in Greece Although Professor Choremis was a distinguished scientific investigator he was primarily a clinician, trained in the great European tradition of clinical paediatrics and perhaps it is as a disciple of Aesculapius and a spiritual descendant of Hippocrates rather than as a scientist that he would wish to be remembered

I was privileged to meet him on only one occasion, during a brief visit that I paid to Athens in 1965 During the course of our discussion I learnt of his interest in the problem of malignant disease in childhood and, when I was asked to contribute to this memorial volume I thought that a clinical article on this theme might be appropriate The following report deals with 5 children with various types of malignant tumour who developed paraplegia in the course of their illness as a result of infiltration of the spinal canal with tumour the tumour having originated in some other part of the body All tumours, both primary and secondary of the spinal cord and appendages are uncommon in children and paraplegia resulting from secondary malignant disease seems to be particularly uncommon. With increasing awareness of malignant disease and its manifestations in childhood this complication may be recognized more frequently in the future and in some cases it may be amenable to treatment which, although only palliative may nevertheless be worth while

Case Reports

1 *Lymphosarcoma*

A 3-year-old boy complained of pain in the shoulders and upper arms and a few weeks later developed a swelling on the right side of his neck. Jaundice developed and gradually deepened A few days before admission to hospital he became unable to move his legs.

On examination he was very ill and deeply jaundiced The liver was enlarged 10 cm below the costal margin, the spleen was just palpable and enlarged lymph nodes could be felt in the abdomen The right cervical lymph nodes were greatly enlarged. He was unable to perform any voluntary movements of his lower limbs but although they were quite flaccid, the ankle and knee jerks were both very brisk and the plantar responses were extensor He was a very fretful, apprehensive child and it was difficult to be sure if there was any associated sensory loss.

On investigation his peripheral blood showed a normal haemoglobin and leucocyte picture The total serum bilirubin was 11-

entirely disappear. Two months later she complained of dizziness and the papilloedema increased. This time she was treated with intrathecal hydrocortisone 10 mg per dose for 3 doses. As this produced no improvement, a fourth course of intrathecal Methotrexate was given, 5 doses in all. She remained unwell and papilloedema steadily increased. As blast cells had reappeared in the C. S. F. a fifth course of intrathecal Methotrexate was given. By now there was also evidence of haematological relapse. Over the next few weeks she developed increasing weakness of her legs progressing to almost complete flaccid paralysis with absence of the tendon jerks in the lower limbs. She was given irradiation to the occiput and the whole spine and within a few weeks she was able to stand and walk again, but the tendon reflexes were slow to return. Improvement was brief and within a few weeks the paraplegia recurred. Further radiotherapy was not advised and so a sixth course of intrathecal Methotrexate was given. Despite the evidence of cord infiltration, the C. S. F. pressure showed a free rise and fall and there was no evidence of a block. Improvement occurred for a few weeks, but signs soon returned and she now had evidence of widespread neurological involvement. There was a left facial paralysis, marked weakness of the right arm and flaccidity [illegible] both lower legs with absence of tendon reflexes. No further active treatment was justified.

4. *Wilms' tumour*

J. S. was first seen shortly before his second birthday. About 2 months previously his mother had noticed enlargement of his abdomen. Some weeks later he developed marked thirst, especially at night time. A month before his first attendance he had been on a visit to New York City with his parents and whilst there he had had a feverish illness. He was diagnosed as having an upper respiratory infection and treated with an antibiotic. On return from the United States he was referred because of increasing enlargement of his abdomen.

The main finding on examination was a large, rounded fixed mass in the left loin. Intravenous pyelography showed marked dilatation of the calyces and of the renal pelvis with generalised enlargement of the left kidney. At laparotomy there was a huge tumour which was adherent to the spleen. It was removed with some difficulty and the spleen was also removed at the same time. The neighbouring glands were not enlarged, but a number were removed for section. They did not show histological evidence of invasion. The renal tumour was confirmed as a Wilms' tumour. Two days before operation he had been started on treatment with Actinomycin D in daily dosage of 12 μgm/kg intravenously. It was planned to give a 10 day course, a total dosage of 120 μgm/kg, but on the ninth day his platelet count suddenly fell from 270,000 per cmm to 90,000 per cmm and treatment was stopped. Over the next few days platelets continued to decrease and he developed extensive purpura of the abdominal wall. He also had glossitis and a macular rash on his lower limbs. He was treated with Prednisolone, 10 mg 3 times daily for a few days and the platelet count rapidly rose.

For the next 6 months he remained very well and regular clinical and radiological examination showed no abnormality. He then developed increasing proptosis of the right eye due to a rapidly growing retro-ocular metastasis. Pain in the abdomen and lower back developed and became increasingly severe. Transient relief was produced by radiotherapy. Loss of power in the legs was first noticed about this time; it gradually increased until he had complete paraplegia of the lower limbs. Sensation was also affected until eventually he had complete anaesthesia of the lower limbs and of the lower abdominal wall. Shortly before this, his abdominal and low back pain had become so severe and was so resistant to analgesic and narcotic drugs that intrathecal injection of phenol was seriously considered. The advent of complete anaesthesia served the same end by producing complete relief of this pain. The subsequent steady deteriora-

On examination he was wasted deeply jaundiced and had dilated veins over the lower chest The abdomen was distended with signs of free fluid A large firm mass was palpable in the right upper abdomen.

At laparotomy a large retroperitoneal tumour was discovered lying mainly under the duodenum and involving its posterior wall It also intimately involved the inferior vena cava and the portal vein Because of its adherence it proved impossible to remove The gall bladder was very distended and, as there was obstruction to the outflow of bile it was anastomosed to a loop of the small intestine A gastroenterostomy was also performed to bypass the tumour

After operation the jaundice rapidly cleared A biopsy specimen proved to be normal pancreas only and it was obvious that this had been taken from the gland stretched tightly over the tumour As further exploration was clearly unjustifiable a precise diagnosis was not obtained

After operation he was referred for radiotherapy to the abdomen and treatment was given over 28 sessions with the maximum dose of 3,500 rads, minimum 3 430 rads of 230 kilovolt irradiation During the course of this treatment the abdominal tumour mass disappeared completely and his general condition improved However whilst improvement was occurring at one site he developed further evidence of disease. A right external rectus paralysis suddenly occurred and X ray of his skull showed multiple osteolytic areas. Deterioration in his general condition recurred and he soon became cachectic It was not thought justifiable to give any cytotoxic therapy but, as the primary tumour could possibly have been lymphosarcoma it was thought reasonable to treat him with corticosteroids in the hope of producing some temporary relief He was discharged home on Prednisolone 25 mg daily

His condition was so poor that it was not thought that he had more than a few days to live However when he was brought back to hospital outpatients 8 weeks later he was reported as being cheerful and having a good appetite. A new development, however was that he now had a complete flaccid paraplegia and was doubly incontinent. As his parents were managing to deal with the difficult nursing problem at home readmission was not advised and he died one week later.

Post mortem examination was not performed.

3 Acute leukaemia

D E. developed acute leukaemia when she was 4½ years old. She was treated with Prednisolone and 6-Mercaptopurine and full remission was obtained in a few weeks. After 7 months maintenance treatment with Mercaptopurine she showed signs of haematological relapse Treatment was changed to Methotrexate 5 mg daily but she soon developed stomatitis, diarrhoea and pancytopenia. Further steroid therapy was given and the Methotrexate was then resumed in dosage of 2.5 mg daily later reduced to 2.5 mg on alternate days. Eight months later she developed headache nausea and vomiting and had bilateral papilloedema. The C S F showed the presence of leukaemic blast cells and she was treated successfully with intrathecal Methotrexate. Three months later papilloedema recurred and blast cells were again found in the C. S. F Eleven further intrathecal injections with Methotrexate were given but although the C S F became clear papilloedema persisted. During the course of the second series of intrathecal injections she developed anaemia and thrombocytopenia. Further steroids were given and maintenance treatment was changed back to 6-Mercaptopurine During the ensuing months she had frequent signs of drug toxicity and intercurrent infection but no frank evidence of relapse Eight months after the second episode of neurological involvement she had recurrence of vomiting and papilloedema and the C S. F again showed the presence of blast cells. Eleven further intrathecal injections of Methotrexate were given with clinical improvement both in symptoms and in the degree of papilloedema although it did not

severe pain, the failure to improve with corticosteroids and Vinblastine all seemed very unusual for histiocytosis. Further skeletal X-rays were now done and they showed considerable progression of all the skeletal lesions. Some of them showed small areas of sclerosis as well as the osteolysis. Another biopsy was now taken from the iliac crest. The histological appearances were of highly malignant tumour destroying bone trabeculae. The tumour consisted of round cells with scanty cytoplasm, large nuclei and numerous mitoses. There was very little differentiation, but in places the arrangement was more compact. In other areas the cells appeared to be lining endothelial spaces. The appearances suggested a malignant sarcoma and the probable diagnosis was "Ewing's sarcoma. This diagnosis was much more in accord with the clinical events. As all efforts at treatment had failed to halt the progress of the disease but it had been possible to relieve her pain, she was discharged home where she died some weeks later.

Post mortem examination was not performed.

Discussion

In a review of the medical literature for the previous 10 years Hamby [4] in 1936 was able to collect 100 cases of tumour of the spinal canal in children. Most of these tumours were primary neural tumours of the cord. Of the small number which were unclassified or grouped as miscellaneous, only one appears to be a definite secondary tumour in that it is listed as a malignant renal tumour. In 1944 Hamby [5] reviewed the literature for the subsequent 10 years and found a further 114 tumours of the spinal canal in children. In this second list none appeared to be metastatic except possibly one listed as an "invasive fibroma. Chloroma is referred to in both series, there having been 8 cases in the first and 1 in the second, but it is not quite clear in the context as to whether this term is used specifically to indicate a locally invasive tumour which is "almost invariably accompanied by acute granulocytic leukaemia" [2]. In 1954 Svien, Thelen & Keith [7] reported 41 cases of intraspinal tumours in children which had been seen over a 20 year period at the Mayo Clinic. The majority of these were primary neural tumours. There had been one case of reticulum cell sarcoma and one lymphoblastoma. There were also two definite metastatic tumours, one from a carcinoma of the thyroid and the other from a Ewing's sarcoma of the sternum.

Paraplegia due to secondary malignant disease is certainly uncommon. In the index to the most recent edition of his authoritative textbook on *Diseases of the Nervous System in Infancy Childhood and Adolescence* Ford [3] lists over 40 causes of paraplegia, but secondary malignant disease is not among them. Presumably as it is more likely to occur at an advanced stage of the disease when the patient's general condition is deteriorating, it is less likely to be drawn to the attention of a neurologist. However on occasion paraplegia may be one of the presenting signs of illness as in Case 1 of the present report and, although in that case there were many other features which enabled a diagnosis to be established, the primary tumour or tumours may be less conspicuous and the patient could then be spared much unnecessary investigation and possible surgical intervention, if the possibility of secondary malignant disease were considered. However unlike cerebral secondaries in adults from undiagnosed bronchial or other primary tumours, all malignant tumours in

tion in his condition was unbearably slow and was made even more distressing by the development of pain above the anaesthetic area. Further metastases became evident including one in the lower jaw which eventually almost filled his mouth and made feeding very difficult. He died 8 months after the tumour was first diagnosed and 3 months after metastases had first become apparent.

5 *Ewing's sarcoma*

A 16 year old girl was referred to Alder Hey Children's Hospital with a history of backache which developed after a fall 18 months previously. The backache at first only lasted a few days, but recurred some months later when she also developed severe pain in the right hip. Skeletal X rays at that time were normal. The pain persisted and X rays one month later showed osteolytic areas in the right femoral neck and in both iliac crests. She was admitted to hospital for further investigation and by now pain became very severe requiring frequent injections of Pethidine. Further investigation at that time added little to the diagnosis. Her white cell count was 11,200 with 70% of polymorphs. The serum alkaline phosphatase was 10.0 K. & A units/100 ml, serum calcium was 9.4 mg/100 ml. Biopsy of one of the bony lesions over the right iliac crest produced yellowish brown, soft gelatinous material which on section, was thought to resemble eosinophilic granuloma of bone. She was treated with Prednisolone, Cyclophosphamide and Methotrexate, but there was no improvement and the pain continued to be severe. Over the next few months she developed increasing proptosis of the left eye.

At the time of admission to Alder Hey Hospital she looked ill and was in considerable pain. There was marked tenderness over the dorsal spine and over the lower ribs. Apart from the left proptosis there were no definite abnormal findings in the nervous system at this stage.

The severity of her pain was unusual for histiocytosis, but re-examination of the scanty histological material seemed to be just about compatible with this diagnosis and, as other forms of treatment had been ineffective she was started on Vinblastine 0.1 mg/kg intravenously increasing weekly up to 0.3 mg/kg. The day after the first injection of Vinblastine she was unable to move her left leg. The knee jerks were absent, the ankle jerks were present and the plantar responses were flexor. Sensation appeared normal. Within a few days there was complete loss of power in both lower limbs and she developed flexor spasms. The plantar responses were now extensor and she had complete anaesthesia of the lower parts of both limbs. She was unable to pass urine and the bladder could only be emptied by compression. At the time of admission to Alder Hey the margins of both optic discs had been slightly blurred but by now there was definite papilloedema. Because of this, it was thought advisable not to perform lumbar puncture. The neurological signs over the lower part of the body meanwhile progressed, so that she had total paresis of the body below the level of D5 and 6 and a sensory loss which was complete below this level.

Pain continued to be very severe and was difficult to control by analgesic drugs. Because of the rapid progression of the paraplegia she was referred for X ray therapy and a total dose of 500 r at the level of D2 to L1 were given through a narrow field. A few days after this, there was slight return of movement in the lower limbs. She showed a withdrawal reflex and slight voluntary movement could be produced. Improvement continued to occur and there was some return of sensation, but useful function was not regained. Meanwhile the swelling over the left eye became much more severe, pushing the eye forward to such degree that recurrent dislocation of the globe was occurring. As this was very distressing to the patient and staff tarsorrhaphy was performed. A small dose of local radiotherapy was also given to the orbit.

The rapid progression of the lesions, the

provement was produced by local radiotherapy but it was only of brief duration. The paraplegia soon recurred and was accompanied by more widespread signs of neurological involvement.

Lymphosarcoma has many affinities with acute lymphatic leukaemia and, in deed, about 20 % of cases of lymphosarcoma terminate with generalised leukaemia. The disease can, therefore be regarded, in many instances, as multicentric in origin and the widespread neurological involvement that occurred in Case 1 was not necessarily metastatic in the strict sense of the term. The evidence of cord compression occurred relatively early in the course of the disease. Although there was some improvement in the neurological signs and symptoms following the course of chemotherapy it was less than might have been expected judging by the improvement that occurred in other parts of the body. It is probable that irreversible damage had occurred to the spinal cord so that only a limited degree of improvement was possible.

So far as the management of paraplegia is concerned, this of course will depend to a considerable extent on the patient's general condition. If the primary disease itself is one that might be expected to respond temporarily to some method of treatment, as in leukaemia or lymphosarcoma, efforts should certainly be made to relieve the cord compression. Local radiotherapy is probably the treatment of choice in such cases although Svien, Th len & Keith [7] advised that laminectomy should be done to relieve the compression to the cord immediately as they think that the slower response to radiotherapy and irradiation itself may produce direct injury to the cord. Laminectomy was not performed in any of the cases in the present series and it is doubtful whether it would have been justifiable in the particular circumstances reported here. The two patients who were treated with local radiotherapy certainly showed some improvement, rapid in the child with leukaemic compression of the cord and much slower in the girl with Ewing's sarcoma. In the other three children the disease was so far advanced that it was not thought justifiable to put them to the discomfort of radiotherapy. In such cases symptomatic management is all that can be done. This includes attention to bladder function, as a distended bladder can give rise to considerable discomfort. At first it may be possible to empty the bladder by regular manual expression. Otherwise the insertion of long indwelling catheter connected directly to a sterile receiver will keep the bladder empty and minimise the risk of infection. If the cord lesion is above the lumbar segments, automatic bladder function may return so that when the bladder is distended to a certain point, it will be emptied in a single act of micturition either spontaneously or on stimulation of the skin of the perineum. If the lesion is in the lumbosacral region, the automatic bladder will not develop although the bladder may regain some tone. Constipation from lack of rectal sensation and from loss of tone in the muscles of defecation may be controlled by small volume enemas although occasional manual removal of faeces may also be needed. Trophic ulceration of the skin may be very troublesome in the early phase of paraplegia. Frequent gentle turning of the patient and careful nursing attention to

children are so relatively uncommon that it is obviously more difficult to maintain the same high index of suspicion.

The spinal cord may be compressed by direct invasion of tumour from without or by blood borne metastatic growths. According to Willis [8] direct invasion of the cord except as microscopic perivascular extension, is unusual It probably occurred however in Case 4 where the spread was directly from the abdomen through the vertebral foramina Abdominal pain and pain in the back preceded the paraplegia and the pain was so severe that chemical destruction of the sensory nerve roots by phenol injections was seriously considered, but was anticipated by subsequent neoplastic destruction of those same roots with complete relief of pain and with the onset of complete anaesthesia Direct spread of tumour probably also occurred in Case 5 Here the secondary tumour was in the vertebrae at the earlier stage when back pain and tenderness were present When the spinal canal became invaded, events moved rapidly so that within a few days of developing weakness in one leg she had a complete paraplegia below the level of D5 and 6 with sensory loss and paralysis of the sphincters. In Case 2 the histological diagnosis was never established. When he was first seen, a posterior abdominal tumour was present and this could have spread to the cord by direct extension However the main tumour mass shrank rapidly during treatment by radiotherapy and there was no evidence of cord involvement at that time When the paraplegia developed some time later there was evidence of metastatic spread elsewhere in the body as shown by the presence of deposits in the skull and it is more likely that the cord compression was due to blood borne metastases rather than to direct spread.

Willis [8] states that secondary tumours of the cord are usually due to blood-borne metastases and that these may be less rare than is supposed but they do not often give rise to clinical symptoms of disease and so they may not always be sought for in routine post mortem examination. In most cases with metastases in the spinal cord multiple cerebral metastases are present as well and these will probably dominate the clinical picture.

The question as to whether focal deposits of cells in the leukaemias should be regarded as metastases has previously been debatable but is largely an academic question Recent studies, such as those of Mathé and others [6] have confirmed that widespread tissue infiltration is a common finding in leukaemia even when the disease appears to be in complete remission. Involvement of the central nervous system is particularly common and has been reported in as many as 30 % of some series of cases. It usually manifests itself by a rise in intracranial pressure with headache, vomiting and papilloedema as the predominant findings. Cranial nerve palsies and convulsions are less common. Signs and symptoms due to compression of the spinal cord are much less common. Ford [3] describes one case of compression of the spinal cord by an extradural mass in a child with acute leukaemia, the mass being composed of leukaemic cells. In Case 3 of the present report there were repeated episodes of neurological involvement but towards the end the cord symptoms were predominant. Considerable im-

rovement was produced by local radiotherapy but it was only of brief duration. he paraplegia soon recurred and was ccompanied by more widespread signs of eurological involvement.

Lymphosarcoma has many affinities rith acute lymphatic leukaemia and, in leed, about 20% of cases of lymphosarcoma terminate with generalised leukaemia. The disease can, therefore, be regarded, in many instances, as multicentric in rigin and the widespread neurological nvolvement that occurred in Case I was not necessarily metastatic in the strict sense of the term. The evidence of cord compression occurred relatively early in the course of the disease. Although there was some improvement in the neurological signs and symptoms following the course of chemotherapy it was less than might have been expected judging by the improvement that occurred in other parts of the body. It is probable that irreversible damage had occurred to the spinal cord so that only limited degree of improvement was possible.

So far as the management of paraplegia is concerned, this of course will depend to a considerable extent on the patient's general condition. If the primary disease itself is one that might be expected to respond temporarily to some method of treatment, as in leukaemia or lymphosarcoma, efforts should certainly be made to relieve the cord compression. Local radiotherapy is probably the treatment of choice in such cases although Svien, Thelen & Keith [7] advised that laminectomy should be done to relieve the compression to the cord immediately as they think that the slower response to radiotherapy and irradiation itself may produce direct injury to the cord. Laminectomy was not performed in any of the cases in the present series and it is doubtful whether it would have been justifiable in the particular circumstances reported here. The two patients who were treated with local radiotherapy certainly showed some improvement, rapid in the child with leukaemic compression of the cord and much slower in the girl with Ewing's sarcoma. In the other three children the disease was so far advanced that it was not thought justifiable to put them to the discomfort of radiotherapy. In such cases symptomatic management is all that can be done. This includes attention to bladder function, as a distended bladder can give rise to considerable discomfort. At first it may be possible to empty the bladder by regular manual expression. Otherwise the insertion of long indwelling catheter connected directly to a sterile receiver will keep the bladder empty and minimise the risk of infection. If the cord lesion is above the lumbar segments, automatic bladder function may return so that, when the bladder is distended to a certain point, it will be emptied in a single act of micturition either spontaneously or on stimulation of the skin of the perineum. If the lesion is in the lumbosacral region, the automatic bladder will not develop although the bladder may regain some tone. Constipation from lack of rectal sensation and from loss of tone in the muscles of defecation may be controlled by small volume enemas, although occasional manual removal of faeces may also be needed. Trophic ulceration of the skin may be very troublesome in the early phase of paraplegia. Frequent gentle turning of the patient and careful nursing attention to

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Hypoglycaemia in Infantile Malnutrition

by E. KERPEL-FRONIUS and E. KAISER

Advance in knowledge of hypoglycaemia in infantile malnutrition was strikingly similar to that of hypoglycaemia in the semistarved adult and in the neonate. Many years passed after the first descriptions of hypoglycaemia before its capital clinical significance was recognized. This sceptical attitude which led to therapeutic nihilism may be explained by the following facts

1) Severe hypoglycaemia is not an obligatory feature of any of these clinical conditions, it occurs only in peculiar cases or at certain stages of the disease.

2) Hypoglycaemia, even if severe is by no means always symptomatic and the symptomatology presents some peculiarities.

3) Attention in these conditions was focused on other at first glance more important or more spectacular metabolic or clinical alterations

With regard to *hunger oedema in the adult* this attitude changed during World War II Although again most investigators devoted their interest to oedema and to protein metabolism, some French authors recognized that hypoglycaemia arising suddenly in extremely emaciated adults may be one of the ultimate causes of death [1].

Neonatal hypoglycaemia, first described by Van Creveld in 1929 [2], had also long been considered a harmless condition, even though Hartman & Jaudon [3] suggested already in 1937 that it may at times cause symptoms. The real clinical significance of this type of hypoglycaemia encountered in cases of intrauterine malnutrition, in infants of diabetic mothers, in prematures and in the respiratory distress syndrome is emerging only from systematic work done in recent years.

Hypoglycaemia in infantile malnutrition has the longest history for the first observations can be traced as far back as the classical period of German Paediatrics preceding World War I [4]. Although Jaso [5] in 1932 called attention to the prognostic significance of decreasing fasting blood sugar levels, the clinical significance of hypoglycaemia was not understood for many years Recent standard textbooks [6 7 8] do not even mention hypoglycaemia in their respective chapters on malnutrition, neither did Trowell [9] take any notice of it in his excellent book on kwashiorkor Abalil in 1950 [10] seems to be one of the first investigators to set the

the skin do much to limit it and the patient could be nursed on some type of alternating pressure mattress [1]. After paraplegia has been present for some weeks, there may be some return of tone in the muscles accompanied by flexor spasms. At this stage the condition of the skin does tend to improve and bed sores are more easily controlled.

Although vigorous efforts to control the primary disease should not be pursued beyond reason and humanity, it is essential to try and preserve the morale both of the child and his family by continued interest and attention to all details of his care and comfort.

Summary

1. Five cases of paraplegia due to secondary malignant disease in children are described.

2. There was one case of generalized lymphosarcoma; one case of acute leukaemia who had recurrent neurological complications, paraplegia developing terminally; one case of metastatic Wilm's tumour; one case of Ewing's sarcoma and one case in which the histological diagnosis was not confirmed, but was probably lymphosarcoma.

3. Tumours of the spinal cord and appendages are uncommon in children and are more often primary than secondary.

4. Spread to the spinal canal may be by direct extension from the abdomen or vertebrae or by blood borne metastases.

5. The management of paraplegia includes care of the bladder, the bowels and of the skin.

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We now come to the description of blood sugar levels found in the severe dry form of malnutrition in young infants. The degree of wasting of the body in these cases was extreme, and it is only inadequately described by percentile deviations of weight from average values for age or for length. Paediatricians working before World War I to whom of course, in this idyllic period in the history of mankind, the physical appearance of the victims of concentration camps was unknown and also unthinkable, stated that such a "physiologic misery" is unparalleled in any other age group in human pathology. It can be affirmed that a deficit of weight for length reaching 30 %, as found in these very young infants, certainly reflects a greater degree of wasting of the body than in older children or in adults.

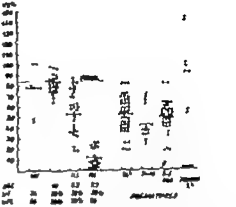


Fig. 1. *Fasting blood sugar levels in marasmic infants and in prematures. KW* = kwashiorkor; *M* = marasmus young children; *MI* = marasmic young infants ("atrophy" and "athrepsia"); *MIS* = young atrophic infants exhibiting symptomatic hypoglycaemia. Prematures 24, 24–48 hours, 3–6 days of age. *RD* preterm, respiratory distress cases within two hours of death. *WFA* deficit of weight for age; *WFL* deficit of weight for length.

Fasting blood sugar levels were in all these cases below the normal mean values. Twenty-one cases had one or more attacks of hypoglycaemia. During the attacks, the blood sugar ranged between 25 and 0 mg/100 ml with a mean value of 11 mg/100 ml. In this danger zone of blood sugar levels there is some overlap with asymptomatic cases: in 4 infants fasting values between 25 and 10 mg/100 ml had not been accompanied by symptoms. It is known that the same phenomenon, i.e. extremely low blood sugar levels with apparent well-being, may be also observed in newborn premature infants. For the sake of comparison Fig. 1 shows blood sugar levels in a number of our premature infants. Although some cases had values below 20 or even below 10 mg/100 ml, only one symptomatic case was observed in this series, an infant of a diabetic mother who had convulsions with a blood sugar level of zero, and who made an uneventful recovery following the intravenous administration of glucose solution. Glycaemia in prematures with respiratory distress raises a special problem. Our data show that in 40 % of all cases preterminal values were below 20 mg/100 ml, and that hyperglycaemia, which is exceptional in normal prematures, also occurred in a high percentage of the cases. This condition, when untreated, leads to mobilisation and preterminal depletion of carbohydrate stores.

Prognostic significance of hypoglycaemia. Low fasting blood sugar levels reflect the severity and the prognosis of malnutrition with higher fidelity than do changes in any other metabolic parameter.

All 10 cases of kwashiorkor and all malnourished gipsy children exhibiting no or only mild hypoglycaemia, survived.

facts in their true light He pointed out that of 20 cases of infantile marasmus 4 exhibited one or more attacks of hypoglycaemia while out of 35 cases of oedematous malnutrition (kwashiorkor) 23 showed hypoglycaemia which in 8 cases appeared to be the cause of death.

We became interested in this question in 1954 when we found that young marasmic infants exhibiting apnoeic spells had severe hypoglycaemia [11] These apnoeic spells announcing impending death from respiratory paralysis were described years ago by Finkelstein [12] and others who felt that they were preterminal signs of an irreversible disintegration of the respiratory center Our observations on eight cases exhibiting apnoeic spells accompanied by hypoglycaemia and promptly relieved by intravenous glucose solution, convinced us that this alarming picture is not irreversible but represents the clinical manifestation of spontaneous hypoglycaemia

This work is an analysis of the incidence the severity the clinical picture and the predisposing factors to hypoglycaemia occurring in the different types and stages of infantile malnutrition

Material and Methods

The material consists of (1) Ten cases of oedematous kwashiorkor like malnutrition occurring in this country exclusively in young gipsy children. (2) Twenty two marasmic gipsy children of about the same age exhibiting, however no oedema or hypoproteinaemia on admission. The aetiology of malnutrition in both these groups was the same, namely low intake of milk animal proteins and of calories, and poor hygienic conditions; (3) Fifty four young infants suffering from the severe, dry form of malnutrition known in classical paediatric terminology as severe atrophy athrepsia or decomposition. Twenty-one infants of the latter group exhibited one or more attacks of symptomatic hypoglycaemia. Malnutrition in these cases was due to inadequate feeding and congenital malformations. Specific coli infection in three quarters of all cases played, however the leading role. About one half of these cases were premature infants.

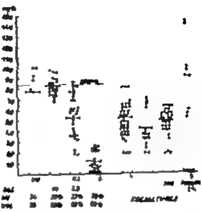
Venous blood drawn after 4–8 hours of fasting or during the hypoglycaemic attack was measured by the method of Somogyi and Nelson [13].

Results

Fasting blood sugar levels in their relation to clinical symptoms Fig 1 showing fasting blood sugar levels found in various types of infantile malnutrition, gives a general impression of the problem. Blood sugar levels in newborn prematures are presented in the figure for comparison.

In ten cases of kwashiorkor like oedematous malnutrition dangerously low blood sugar levels or clinical symptoms referable to hypoglycaemia were never encountered. The same is true of the next group of gipsy children of about the same age exhibiting no oedema on admission. It should be pointed out that the degree of malnutrition in these cases, although severe was not extreme Weight compared to that of normal infants of the same age showed a deficit of 34–35 %, it was smaller when weight was compared to that of normal children of the same length however This indicates that in these infants the percentile deviation from average weight for age is only in part due to emaciation and that stunted growth occurring invariably in malnutrition of long duration is also important

We now come to the description of blood sugar levels found in the severe, dry form of malnutrition in young infants. The degree of wasting of the body in these cases was extreme, and it is only inadequately described by percentile deviations of weight from average values for age or for length. Paediatricians working before World War I to whom, of course in this idyllic period in the history of mankind, the physical appearance of the victims of concentration camps was unknown and also unthinkable, stated that such a "physiologic misery" is unparalleled in any other age group in human pathology. It can be affirmed that a deficit of weight for length reaching 30 %, as found in these very young infants, certainly reflects a greater degree of wasting of the body than in older children or in adults.



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Fasting blood sugar levels were in all these cases below the normal mean values. Twenty-one cases had one or more attacks of hypoglycaemia. During the attacks, the blood sugar ranged between 25 and 0 mg/100 ml with a mean value of 11 mg/100 ml. In this "danger zone" of blood sugar levels there is some overlap with asymptomatic cases: in 4 infants fasting values between 25 and 10 mg/100 ml had not been accompanied by symptoms. It is known that the same phenomenon, i.e. extremely low blood sugar levels with apparent well-being, may be also observed in newborn premature infants. For the sake of comparison Fig. 1 shows blood sugar levels in a number of our premature infants. Although some cases had values below 20 or even below 10 mg/100 ml, only one symptomatic case was observed in this series, an infant of a diabetic mother who had convulsions with a blood sugar level of zero and who made an uneventful recovery following the intravenous administration of glucose solution. Glycaemia in prematures with respiratory distress raises a special problem. Our data show that in 40 % of all cases preterminal values were below 20 mg/100 ml, and that hyperglycaemia, which is exceptional in normal prematures, also occurred in a high percentage of the cases. This condition, when untreated, leads to mobilisation and preterminal depletion of carbohydrate stores.

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All 10 cases of kwashiorkor and all malnourished gipsy children exhibiting no or only mild hypoglycaemia, survived.

TABLE 1 *Weight deficits blood sugar levels and mortality rates in infantile malnutrition.*

	Number of cases	% weight deficit for length	Blood sugar (mg/100 ml) Max	Mean	Min	Mortality rate ( )
Kwashiorkor	10	[illegible]	100	77	45	0
Dystrophy	[illegible]	23	[illegible]	82	6	0
Marasmic infants, blood sugar > 30 mg/100 ml	18	[illegible]	81	63	51	16.6
Marasmic infants, blood sugar < 50 mg/100 ml	13	[illegible]	30	34	14	[illegible]
Marasmic infants with sympt hypoglycaemia	1	29	[illegible]	11	0	[illegible]

Thus the presence or absence of oedema carries no reliable prognostic value In the young marasmic infants the death rate increased with decreasing fasting blood sugar levels and one half of the infants presenting symptomatic hypoglycaemia were ultimately lost Although the first attacks in those cases were relieved promptly by intravenous administration of glucose solution in 7 cases we were late in treating recurring attacks 4 infants died presumably from septicaemia due to coli infection.

Signs and symptoms The early signs and symptoms of hypoglycaemia seen in adults are absent or cannot be ascertained in malnourished infants. Table 2 summarizes the symptoms observed in our cases.

Deathly pallor or an ash grey colouring of the face was a constant sign In 10 out of the 21 first attacks the patients exhibited apnoeic spells mostly accompanied

TABLE 2 *Symptoms of hypoglycaemia in malnourished infants*

Number of cases	21
Pallor	1
Apnoeic spells	10
Hypothermia	7
Rolling of the eyes	4
Convulsions	1

by slowing of the pulse rate. Convulsions appeared only exceptionally in severely malnourished young infants.

Conclusive proof that this condition resulted from hypoglycaemia was the effect of intravenous glucose solution. This was practically always a dramatic effect the colour and the general condition greatly improved while the respiratory and pulse rate increased (Fig 2)

Predisposing factors The tendency to spontaneous hypoglycaemia is revealed by the shape of the blood sugar curve during fasting Fig 3 shows the mean and the extreme values of five infants who a few days preceding this study exhibited attacks of spontaneous hypoglycaemia.

Blood sugar levels studied at hourly intervals in normal or not extremely malnourished infants remained unchanged for six hours following the last meal In many cases of extreme malnutrition blood sugar decreased progressively the slope of the fasting curve being steepest 3–4 hours following the last meal

The degree of hypoglycaemia as well as the appearance of clinical symptoms were roughly correlated directly to the degree of malnutrition as expressed by the deficit of weight for length (Fig 4)

Fig. 2

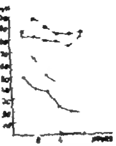

Fig. 3

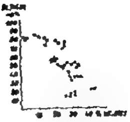

Fig. 4

Fig. 2. *Effect of intravenous glucose administration on hypoglycaemic symptoms.*

Fig. 3. *Effect of fasting on glycaemia in normal, moderately and severely malnourished infants.* ○— —○ = normal; —— = moderately malnourished infants; ●—● and —— = severely malnourished infants.

Fig. 4. *Fasting blood sugar levels in infants as function of weight deficit for length.* Closed circles represent symptomatic cases.

Attacks of spontaneous hypoglycaemia sometimes appeared in the group with weight deficits between 25–40%. In a great number of infants with this degree of malnutrition fasting blood sugar did, however, not fall to dangerous levels.

Analysing the factors predisposing to hypoglycaemia in the neonate, Cornblath [14] drew attention to the high brain/liver ratio in this age group. He pointed out that the relatively large brain is the chief user of blood glucose, the relatively small liver being the endogenous source of blood glucose. Organ proportions in malnutrition change in the same unfavourable direction, as shown in thirteen of our extremely malnourished young infants (Fig. 5).

Liver weight is only [illegible]0% of that in controls of the same age, while the brain appears to be almost unaffected by malnutrition. This results in a brain/liver ratio of about 5 as contrasted to that of 3.6 found in controls. The same change takes place in the malnourished adult. We calculated from available organ weights [15] the brain/liver ratio of victims of the Warsaw Ghetto during World War II, it was more than double that of the normal adult. While increased brain/liver ratio certainly appears to predispose to hypoglycaemia, its effect is felt only in cases with undermined blood sugar regulation. This conclusion is warranted by two facts: (1) low blood sugar levels and symptomatic hypoglycaemia occur only in some, but not all extremely emaciated subjects and (2) stabilization of glycaemia in individuals with symptomatic hypoglycaemia may occur before the beginning of catch-up growth, therefore, without change in the brain/liver ratio (Fig. 6).

A possible factor predisposing to or provoking hypoglycaemic attacks may be *intestinal malabsorption of carbohydrates*. In an earlier study on 02 cases of malnutrition, severe impairment of lactose splitting was found in about one quarter of the cases, while malabsorption of sucrose or monosaccharides was rare and seldom severe [16]. Since our oedematous protein-calorie malnutrition cases, though poor absorbers of lactose, did not exhibit hypoglycaemia, we may surmise that carbohydrate malabsorption is not a decisive

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Dystrophy	23	[illegible]	10	8	[illegible]	0
Marasmic infants, blood sugar > 50 mg/100 ml	18	29	81	68	51	16.6
Marasmic infants, blood sugar < 50 mg/100 ml	[illegible]	[illegible]	[illegible]	34	14	[illegible]
Marasmic infants with sympt hypoglycaemia	21	39	23	11	0	[illegible]

Thus the presence or absence of oedema carries no reliable prognostic value In the young marasmic infants the death rate increased with decreasing fasting blood sugar levels and one half of the infants presenting symptomatic hypoglycaemia were ultimately lost Although the first attacks in these cases were relieved promptly by intravenous administration of glucose solution, in 7 cases we were late in treating recurring attacks; 4 infants died presumably from septicaemia due to coli infection

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Deathly pallor or an ash grey colouring of the face was a constant sign. In 19 out of the 21 first attacks the patients exhibited apnoeic spells mostly accompanied by slowing of the pulse rate Convulsions appeared only exceptionally in severely malnourished young infants.

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Number of cases	21
Pallor	21
Apnoeic spell	19
Hypothermia	7
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The degree of hypoglycaemia as well as the appearance of clinical symptoms were roughly correlated directly to the degree of malnutrition, as expressed by the deficit of weight for length (Fig 4)

cotrophine or adrenal steroids. A treatment of 10 days increased and stabilized the fasting blood sugar levels in most of our symptomatic cases. In three cases, however this effect was only transitory and recurrences of symptomatic hypoglycaemia required renewal of treatment.

Discussion

The literature on the incidence the clinical significance and pathogenesis of hypoglycaemia in malnutrition contains many contradictions. In kwashiorkor some authors found low [10 17] and others [18, 19] normal or nearly normal blood sugar levels. *Attempts to elucidate the* origin of hypoglycaemia by studying the response to epinephrine and insulin, as well as glucose tolerance tests *yielded* contradictory results. Liver glycogen has been studied but in few cases [10 20] and only exceptionally in cases exhibiting hypoglycaemia *(10)*

The explanation of these contradictions may be found in the following facts: the *breakdown of blood sugar regulation* is by no means a metabolic change occurring in all cases of malnutrition The most important predisposing factor is a severe degree of wasting of the body This, however is not necessarily reflected by the low body weight of the patient as compared to that of *normal infants of the* same age, i e by the index generally used to express the severity of malnutrition. We have called *attention to this fact in* an earlier investigation [21], *indicating* that owing to the arrest of growth, many of the low weight for age infants are small rather than extremely thin. Fig 4 shows, however that the tendency to hypoglycaemia appeared only in infants in whom the weight deficit for length exceeded 20-25% of their initial weight. Such young infants lost practically all their subcutaneous fat and clinically they looked extremely marasmic. As to kwashiorkor we feel that the practice to consider the appearance of oedema and the low weight for age index as criteria of *the severity of protein-calorie* malnutrition explains contradictory reports about the incidence and the severity of hypoglycaemia. Oedema, although a spectacular symptom, does not indicate that malnutrition is in its severest phase Experience shows that protein-calorie malnutrition *which is severe enough to* cause conspicuous changes in certain parameters, namely hypoproteinaemia, oedema decreased *activity* of pancreatic enzymes and of *intestinal* lactose splitting ability [21] is not by necessity associated with simultaneous breakdown of blood sugar *regulation. It should be pointed out* that although our cases of kwashiorkor exhibited all the alterations enumerated above, they were neither extremely emaciated, nor hypoglycaemic. Thus, we assume that the hypoglycaemic cases of kwashiorkor described by some of the authors who studied this *problem, must* have been not only oedematous, but also extremely wasted. This assumption is in *keeping with the* experience *with fatal* cases of hypoglycaemia in malnourished adults during World War II Wasting in *all these cases* was extreme and comparable to that seen in our young atrophic and hypoglycaemic infants.

While an extreme degree of emaciation and consequent changes *in organ* proportions should be considered as important

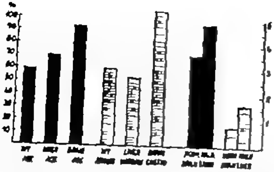

Fig 5 Brain/liver weight and ratio in hypoglycaemic marasmic infants and in semi-starved adults 100% = normal weights for age Black columns = infants. The two pairs of columns on the right show the brain/liver ratios in normal and in malnourished individuals respectively

factor in the origin of hypoglycaemia Evidence in favour of this point is added by observations made in three cases of young coli infected marasmic infants in whom lactose and sucrose absorption following the oral administration of 2 5 g sugar per kg body weight was studied during severe hypoglycaemia

Increments in blood sugar in all these cases were satisfactory and hypoglycaemia was relieved both by lactose and by sucrose loading Defective splitting or absorption of carbohydrates, may be a

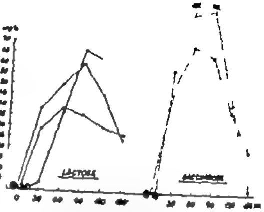

Fig 7 Effect of lactose or saccharose loading in hypoglycaemic malnourished infants Abscissa = time after loading; ordinate = increments in blood sugar levels; numbers in circles represent initial blood sugar values.

contributory factor in some cases, but it is certainly not the decisive mechanism promoting hypoglycaemia (Fig 7)

Effect of ACTH or adrenal steroids on hypoglycaemia

Fig 8 shows that the sharp decrease in blood sugar during fasting can be counteracted by the administration of corti

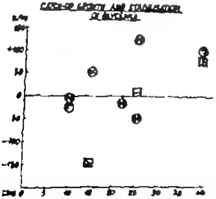

Fig. 6. *Catch-up growth and stabilisation of glycaemia.* Abscissa = days on rehabilitory diet. Ordinate = gain or loss of weight. Numbers represent fasting blood sugar values; squares = recurrent symptomatic hypoglycaemia.

Fig 8

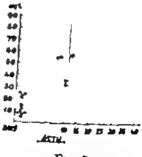

Fig 9

Fig 8. *Effect of ACTH on fasting blood sugar levels* Wt = body weight in gms.

Fig 9 *Effect of ACTH in symptomatic cases of hypoglycaemia* Black dots = blood sugar during hypoglycaemic attacks.

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factors predisposing to low blood sugar levels the dramatic rapidity with which hypoglycaemia and an alarming clinical picture sets in suggests low glycogen reserves and a slow rate of gluconeogenesis. The sudden breakdown of blood sugar regulation follows intestinal infections and stresses always appearing during the acceleration of the wasting process. On the *other hand, this* severe disturbance is to a certain extent self limited which disappears following the elimination of infection and the introduction of a proper diet even before catch up growth sets in. It is only to be expected that liver glycogen *content epinephrine* insulin and glucose tolerance tests will yield variable results depending upon the phase of the disease during which these studies were undertaken [18 19 22 23] In brief the study of blood sugar regulation in malnutrition should be approached as a dynamic not *as a static problem* Unequivocal results can only be expected when carbohydrate metabolism is studied comparatively in the hypoglycaemic and in the non hypoglycaemic phase of malnutrition. Such studies are now in progress.

Summary

The incidence the clinical significance *and the* factors predisposing to hypoglycaemia were studied in 84 malnourished *infants.* Predisposing factors were young age intestinal infections extreme wasting of the body the deficit in weight exceeding 25 % as compared to normal infants of the same length and even brief periods of fasting Older oedematous infants, if not extremely marasmic were not hypoglyc*aemic.* Malabsorption of carbohydrate does not play a leading role in eliciting hypoglycaemia since severe hypoglycaemia was also observed in cases in whom the ability to split disaccharides was preserved.

The prominent clinical symptoms at blood sugar levels between 25 and 0 mg/100 ml were pallor and apnoeic spells, while convulsions were exceptional. There was a prompt response to intravenous glucose and recurring attacks were generally prevented by frequent feeding and by the administration of corticoids. Some cases *exhibiting* very low blood sugar levels remained asymptomatic Fasting blood sugar levels were found to be of great prognostic significance

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Case number	Sex and age (years)	Onset of symptoms before admission, months	History and symptoms	Course	Death following admission (months)	CSF	Lange
1	Male 5 years	1	Frequent falls, head drop attacks, rythmic involuntary movements, intellectual deterioration	Rapid deterioration, spastic tetraplegia, coma	2	Normal	—
2	Male 6 years	2	Forgetfulness, disturbed behaviour head drop attacks with revulsion of the eyes, frequent falls, variable repetitive jerking movements, intellectual deterioration	Rapid deterioration, drowsiness, hypertonia, coma	1	Protein: 40 mg/100 ml. Glucose: 80 mg/100 ml. Cells 55/e mm	—
3	Female 6 years	1½	Akinetic spells with unexpected falls, rythmic myoclonic seizures, left sided myoclonus, epilepsia partialis continua, involvement of mental and psychic functions	Dementia, leftsided myoclonus. Seven months later spastic quadriplegia, coma	8	Protein: 30 mg/100 ml Glucose: 40 mg/100 ml Cells: 40/e.mm	4332100000
4	Male 8 years	4	Memory disturbances, clumsiness, head drop attacks, rythmic myoclonic seizures, mental deterioration	Rapid deterioration, dementia hypertonia, coma	1½	Protein: 25 mg/100 ml Glucose 67 mg/100 ml Cells 6/e.mm	1110000000
5	Male 11 years	6	Difficulties in school work, head drop attacks, G.M. seizures, rythmic involuntary movements, intellectual deterioration	Progressive deterioration. Left-sided spasticity	5	Protein: 44 mg/100 ml Glucose: — Cells 4/e.mm	5543321000
6	Male 9 years	3	Memory disturbances, difficulties in school work, clumsiness, staggering spells with falls, head drop attacks, intellectual deterioration	Discharged few days later	7	Protein: 38 mg/100 ml Glucose: 49 mg/100 ml Cells. 9/e.mm	5433110000
7	Male 6 years	3	Memory disturbances, apathy diminution of scholastic abilities, clumsiness, staggering spells with falls, rythmic involuntary movements	Rapid deterioration, fixed face, dementia, leftsided myoclonus, semi-coma, spastic quadriplegia	6	Protein: 45 mg/100 ml Glucose: 82 mg/100 ml Cells: 10/e.mm	5432100000
8	Male 5 years	1	Head drop attacks, spontaneous rythmic movements	Progressive deterioration. Seven months later dementia	Unknown	Protein: 18 mg/100 ml Glucose: 60 mg/100 ml Cells 118/e.mm	5433110000

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From the Pediatric Clinic of Athens University

Clinical Considerations, EEG and EMG Studies, in Subacute Sclerosing Leucoencephalitis

by V KYRIAKIDOU

The clinical picture of subacute sclerosing leucoencephalitis [6 7] (SSLE) which includes intellectual deterioration, involuntary repetitive movements and a subacute course is very characteristic The demonstration of rythmic complex discharges in the electroencephalogram (EEG) [2 3 8, 10 11 12] coinciding with the involuntary movements provided a valuable adjunct to the premortem diagnosis of the disease The results of several studies [1 15] have left no doubt that the Van Bogaert [14] SSLE the Dawson inclusion body encephalitis [4 5 13] and the Pette-Döring [9] panencephalitis are one and the same condition.

In this paper clinical observations the EEG and electromyographic (EMG) phenomena are reported from 8 cases seen at the Pediatric Clinic of Athens University during the last 3 years.

Methods

In all 8 patients EEG tracings were recorded repeatedly during the course of the disease. EMG studies with surface electrodes were made in two patients. Both EEG and EMG recordings were performed on an 8 channel Alvar apparatus. 21 electrodes were used contact being made through a saline jelly Bipolar and average reference recordings were used. The paper speed varied from 1.5 cm to 3 cm/sec The constant time was in the order of 0.3 sec for the EEG and 0.1 for the EMG

Results

Clinical observations

These are summarized in Table 1 In the first stage of the insidious onset of SSLE the clinical picture consisted of early and progressive intellectual deterioration and severe involvement of all psychic functions diminution of scholastic ability short attention span, apathy as well as memory disturbances. These symptoms sometimes noted only in retrospect were accompanied or followed by episodic staggering clumsiness drop attacks or convulsive like episodes.

Five patients (cases 1 2 3 6 7) had gait difficulties caused by frequent fal[ls] Head drop attacks were noticed in [.] patients (cases 1 2 4 5 6 8) with rev[ul]sion of the eyes in one (case 2) The attacks were mistaken for akinetic [sei]zures. Grand mal fits occurred in o[ne] patient (case 5) Focal myoclonic jerki[ng] in the form of epilepsia partialis contin[ua] developed in two patients (cases 3 and [.]

Later variable rythmic involunta[ry] movements appeared in all patients. The

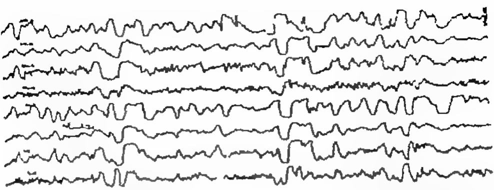

Fig. 2a. Case 7: Male, 6 years. EEG on admission, in waking state. On relatively slow record, with some preservation of rythms up to 7 c/s, periodic discharges, 2 per second, are represented, consisting of high potential very slow irregular waves, preceded by a diphasic, slow sharp wave. (Paper speed 3 cm/s.)

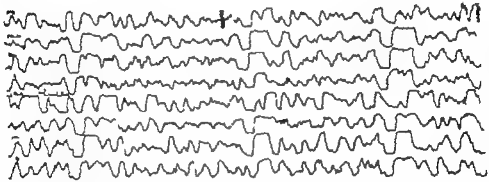

Fig. 2b. Same patient, 4 days later. The background activity is slower. The discharges are clear and large with nearly the same periodicity and shape.

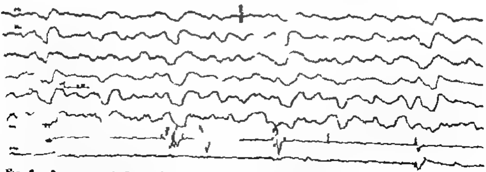

Fig. 2c. Same patient, 3 months later. Semicoma, continuous jerking movements on the left, tetraplegia, rythmic myoclonic seizures, dementia. EEG: On very slow background only the rythmic EEG complexes are distinguishable. EMG of the left and the right biceps. EMG discharges on the left correspond to the beginning of the EEG complexes.

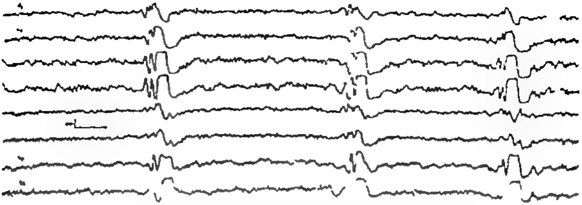

Fig 1 Case 5: Male 11 years. EEG on admission, in waking state. Rythmic discharges, 9 per second on a relatively organized backround activity with slight asymmetry and a more clearly defined alpha rythm at right. Note the similarity of complexes, consisting of burst of high voltage sharp waves followed by a slow wave (Paper speed 1.5 cm/s.)

were classified as follows (a) stereotyped repetitive jerking movements of isolated muscles groups. (b) widespread, spontaneous rythmic myoclonic-like seizures, repeated fairly constantly at 5 10 or 20 seconds and coinciding with the EEG rythmic complexes These seizures could be provoked by stimulation and were abolished in deep sleep or narcosis, during which the EEG complexes persisted (c) Fine continuous tremor limited to one or more hypertonic limbs.

The ocular fundi were normal in all but 1 patient who showed pigmentary macular degeneration.

In a later stage all patients deteriorated to almost complete dementia Neurologic examination at this time revealed semi coma or coma with hypertonia and spastic quadriplegia sometimes with focal neurological signs. Seven patients died within 2–8 months following hospitalizations

EEG and EMG studies

In each case rythmic complexes were seen at intervals of 5 to 20 seconds or 4 to 12 times a minute they invariably coincided with the stereotyped involuntary movements (Figs. 1 and 2a b c) In one patient EEG discharges disappeared temporarily while jerks persisted. There was some individual variation in the pattern of the EEG discharges; however in each patient the complexes were always the same The usual form of the rythmic complexes consisted of bursts of high voltage slow waves preceded by one two or more rapid or slow sharp mono- or diphasic waves on a more or less disorganized background A period of relative silence sometimes followed the complex. As the disease progressed the basic tracing became slower and usually showed complete disorganization with very slow irregular background activity Rythmic discharges persisted but became less evident so that they sometimes became hardly distinguishable from the generalized irregular slow waves. In deep sleep spontaneous jerking ceased but the rythmic complexes not only persisted, but were more clearly defined The same activation

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of the periodic discharges appeared to occur during photic stimulation.

The onset of the EMG discharges coincided with the beginning of the EEG complex (Fig 2c)

Comments

Since autopsy was refused in all cases, pathological confirmation of the diagnosis is lacking. This is why only typical cases have been included in this report. The present clinical and EEG observations indicate that diagnosis of SSLE is not difficult. Early mental deterioration and the occurrence of repetitive involuntary movements, coinciding with the rythmic EEG complexes, are the main features of this disease. The strongly left-zonal or paretic colloidal gold curve (Lange) in the cerebrospinal fluid is a valuable laboratory test. Important diagnostic criteria are also provided by the age and sex of the patient, the subacute course and the fatal outcome.

The assumption that involuntary movements of SSLE are different from myoclonic seizures is open to question. Some authors believe [7, 8] that the myoclonic spell in SSLE begins as abruptly as the true myoclonic jerk, but that unlike the latter it is longer and ceases gradually.

The EEG study revealed rythmic complexes in repeated recordings in all but two of our patients. In one case (case 1) periodic components disappeared temporarily while jerks persisted. In the second patient the first EEG taken 2 months after the onset of symptoms, was normal. At this time the child presented akinetic spells with memory and behaviour disturbances. Two months later he had EEG changes which were characteristic of SSLE. The constant relationship between the repetitive movements and the periodic EEG discharges was invariably seen in our patients. During sleep or photic stimulation some activation of the periodic events was noted.

Summary

Clinical considerations, as well as EEG and EMG studies from 8 patients, 7 males and one female 5 to 11 years old, with SSLE are reported.

Mental deterioration, involuntary rythmic movements coinciding with periodic EEG complexes, were constant findings. In all cases the EEG showed periodic discharges at intervals of 5 to 20 seconds, on a more or less disorganized background activity. The EMG study revealed that the action potentials of the involuntary movements occurred at about the beginning of the periodic EEG changes.

In deep sleep spontaneous jerking ceased while the EEG complexes persisted.

Some activation of the rythmic discharges in the EEG appeared to occur during sleep and photic stimulation.

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neat un liquide opalescent. Elles siègent sur les piliers antérieurs du voile du palais, sur la luette et, plus rarement sur les amygdales et la paroi postérieure du pharynx, très exceptionnellement sur la face interne des joues et la langue. Elles sont bilatérales, irrégulièrement réparties de part et d utre de la ligne médiane, isolées et non groupées, jamais confluentes; elles peuvent ne siéger que d'un côté. Elles sont en petit nombre 5 à 6, une quinzaine u plus.

L évolution de ces lésions est très rapide en quelques heures, 48 heures au plus, elles passent de la phase enanthémateuse à la phase vésiculaire, des vésicules à liquide clair aux vésicules à liquide louche ou pustules, et à la phase ulcéreuse. Leur rupture laisse place à des exulcérations ou ulcérations petites, arrondies, à fond gri sâtre.

L engorgement des ganglions satellites (sous-angulo-maxillaires) est nul ou seulement modéré.

L'hémogramme est normal, sauf en cas d'infections bactériennes surajoutées.

A côté des formes typiques on peut observer des formes typiques

— formes seulement érythémateuses, sans vésicules ni ulcérations.
— formes fébriles pures, réduites à des signes généraux.
— formes accompagnées d éruptions cutanées.
— formes compliquées de troubles digestifs vec diarrhée, ou de parotidite [3], ou d accidents laryngés simulant le croup ou encore d'acci dents méningo-encéphalitiques.

On tend à admettre la possibilité de formes cliniquement asymptomatiques (porteurs sains de virus) ne donnant lieu qu à des modifications sérologiques (ascension des anticorps neutralisants).

Le diagnostic clinique dans les formes typiques, est facile. On éliminera sans peine le muguet, les angines érythémato-*pultacées*, l énanthème de la varicelle. Marfan a bien montré les caractères qui séparent ce qu il appelait l « angine pustuleuse » de l angine et de la stomatite herpétique, — ainsi que ceux qui la distinguent de ce que les classiques décrivent sous le nom d angine aphteuse, expression qui couvre, chez l'homme un syndrome dont l étiologie est encore mystérieuse.

Le diagnostic virologique est basé sur l'isolement du virus. Les enquêtes systématiques effectuées à l occasion de certaines épidémies, ont d une manière quasi constante, permit l'isolement de virus Coxsackie du Groupe A. Le type le plus fréquemment rencontré a été le type 4, mais on a observé également les types 1 2, 3 5, 6 7 8, 9 10, 16 et 22. L'isolement se fait facilement dans les selles ou la salive, plus difficilement à partir de prélèvement pharyngés, car dans la gorge le virus ne persiste guère plus de trois jours.

L ascension des anticorps déviant le complément ou des anticorps neutralisants tteint un taux élevé dans le mois qui suit l'infection, permettant ainsi un diagnostic rétrospectif. Ce taux élevé persiste plusieurs semaines, voire 3 à 4 mois.

Les recherches virologiques les plus récentes ont compliqué le problème étiologique. L ascension simultanée des anticorps antipoliomyélitiques n est pas ex ceptionnelle mais sans doute s agit-il ici d une simple coïncidence. Par contre dans certaines épidémies d'herpangine, on a invoqué la responsabilité des virus Cox

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L herpangine ou angine de Marfan-Zahorsky

par MARCEL LELONG

Le terme d « herpangine » a été créé aux États-Unis en 1924 par J Zahorsky [6] pour isoler une entité clinique distincte de l angine herpétique et à laquelle il rattachait des faits qu il avait publiés en 1920 mais qu à l époque il avait reliés à l herpès. En février de la même année Marfan [5], à l aide de 9 cas personnels, avait décrit sous le nom d « angine pustuleuse » un type d angine qu il séparait nettement de l angine herpétique d une part et de l angine aphteuse d autre part. A ces deux auteurs nous devons donc l individualisation clinique du syndrome. Des deux termes proposés aussi mal choisis l un que l autre c est celui d'herpangine qui a été retenu par l usage international malgré la confusion regrettable qu il laisse persister avec l herpès Aussi serait-il mieux de parler d angine de Marfan–Zahorsky

C'est à R J Huebner *et coll.* [4] que revint le mérite d avoir par des études épidémiologiques et virologiques poursuivies méthodiquement dès 1949 démontré la responsabilité des virus Coxackie A. Par la suite leurs conclusions ont été vérifiées dans de nombreux pays d Amérique, d Europe et d Asie. En France J Gerbeaux *et coll.* [2] ont présenté en 1960 une étude clinique et virologique d une épidémie hospitalière avec isolement d'un virus Coxackie A4

L'herpangine est une maladie saisonnière et surtout une maladie d été elle s observe le plus souvent de Juin à Octobre Elle frappe avec prédilection les enfants de moins de trois ans. Il en existe des cas sporadiques, mais tous les auteurs soulignent son caractère épidémique. La plupart des épidémies concernent des collectivités : hôpitaux crèches, pouponnières, ou familles. La durée de l incubation est assez courte 3 à 5 jours.

Dans sa forme typique la maladie débute brusquement par une montée fébrile à 38° 5–39 ou même 39 –40°C. Cette fièvre persiste deux ou trois jours. Elle peut s accompagner de céphalée, de vomissements de douleurs thoraciques ou abdominales, de myalgies, et même de convulsions.

Dans les deux tiers des cas, la dysphagie attire l attention vers la gorge A l examen, celle-ci montre des lésions caractéristiques. Sur un fond d érythème pharyngé diffus, plus intense sur les bords libres du voile du palais et sur la luette se voient des vésicules arrondies hémisphériques ou même coniques, de 1 à 2 mm de diamètre. Entourées d une petite auréole rouge elles sont de couleur blanc grisâtre et contien

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Body Temperature of the Newborn Infant in Relation to Placental Transfusion[1]

by WILLIAM OH,[2] and JOHN LIND

When clamping of the umbilical cord is delayed at birth, the newborn infant receives a sizable amount of placental blood transfusion [9, 26]. Measurement of blood volume in these *infants* during the first 30 minutes after birth revealed that this placental blood transfer could amount to at least 33% of the infant's original blood *volume [21, 27]*. The blood volume difference resulting from early or late cord clamping has been shown to significantly influence the normal hemodynamic changes immediately after birth [4, 5, 18, 19, 20].

This communication deals with the body and skin temperature changes of infants with early or late cord clamping during the first 5 days of life.

Material and Methods

The subjects of this study were thirty-six newborn *infants* delivered vaginally at the Sodra Barnbordshuset (Southern Maternity Hospital) Stockholm, Sweden, after 38 to 42 weeks *of gestation. The course of* the pregnancies, labors and deliveries were uncomplicated. The average duration of labor was 10 hours and 36 minutes (range 5 to 23 hours); 15 of the mothers received intermittent inhalation of short duration of nitrous oxide ½ to 3 hours before delivery. There were 17 male and 19 female infants with an average birth weight of 3,560 g (range 2,900 to 4,520 g). All infants had an Apgar score [1] of 8 to 10 at 5 minutes of age. None of the infants developed any illness or complication during the period of observation.

In one study skin temperatures of 30 infants were serially followed from 5 minutes to 5 days of life. These *infants* were divided into two groups according to the time their umbilical cords were clamped at birth (the delivery of the infant's buttocks was considered as the time of birth).

Group I. Late clamped group (*16 infants*). Cords were clamped after the umbilical arterial pulsation had stopped. Average time of clamping was 3 minutes 48 seconds after birth (range 2 minutes 30 seconds to 5 minutes).

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From the Teratology Research Unit Swedish Medical Research Council, Pediatric Clinic, Karolinska Sjukhuset and Sodra Barnbördshuset, Stockholm, Sweden

Body Temperature of the Newborn Infant in Relation to Placental Transfusion[1]

by WILLIAM OH, and JOHN LIND

When clamping of the umbilical cord is delayed at birth the newborn infant receives a sizable amount of placental blood transfusion [9, 26]. Measurement of blood volume in these infants during the first 20 minutes after birth revealed that this placental blood transfer could amount to at least 32% of the infant's original blood volume [*1 *7]. The blood volume difference resulting from early or late cord clamping has been shown to significantly influence the normal hemodynamic changes immediately after birth [4 5 18, 19 20].

This communication deals with the body and skin temperature changes of infants with early or late cord clamping, during the first 5 days of life.

Material and Methods

The subjects of this study were thirty-six newborn infants delivered vaginally at the Sodra Barnbordshuset (Southern Maternity Hospital) Stockholm, Sweden, after 38 to 42 weeks of gestation. The course of the pregnancies, labors and deliveries were uncomplicated. The average duration of labor was 10 hours and 36 minutes (range 5 to 23 hours); 15 of the mothers received intermittent inhalation of short duration of nitrous oxide ½ to 2 hours before delivery. There were 17 male and 19 female infants with an average birth weight of 3,550 g (range 2,900 to 4,020 g). All infants had an Apgar score [1] of 8 to 10 at 5 minutes of age. None of the infants developed any illness or complication during the period of observation.

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TABLE 1. *Sex, birth weight, duration of labor, time of cord clamping and venous hematocrits of 36 newborn infants with early and late cord clamping*

		Late clamped group	Early clamped group
Number of infants		22	14
Sex			
Male		11	8
Female		11	6
Birth weight (grams)	Mean	3,580	3,440
	Range	2,900 to 4,600	2,090 to 4,520
Duration of labor	Mean	11 hr 30 min	9 hr 34 min
	Range	6 to 22 hr	5 to 18 hr
Time of cord clamping	Mean	3 min 46 sec	9 sec
	Range	2 min 30 sec to 5 min	2 sec to 20 sec
Venous hematocrit of age ½ hr	Mean	66.3	62.0
	±S.D.	±4.6	±3.9

Difference is statistically significant (p 0.003).

TABLE 2. *Palmar and heel skin temperature changes in 6 newborn infants from birth through 15 minutes of age.*

	Minutes after birth	0	¼	½	1	2	3	4	5	6	7	8	9	10	15
Palm	Mean	34.4	34.5	34.5	34.0	32.6	32.6	31.5	31.5	31.4	30.6	30.3	30.1	29.7	29.4
	Range														
	Min.	34.0	34.2	34.0	32.6	31.8	31.0	30.8	30.8	30.4	29.6	29.8	28.4	28.6	28.3
	Max.	35.0	34.8	34.8	35.0	33.6	33.1	32.6	32.0	32.0	32.4	32.4	32.1	32.1	30.8
Heel	Mean	33.6	34.4	33.8	32.7	31.8	31.7	30.4	30.0	30.2	29.9	29.8	29.7	29.8	29.9
	Range														
	Min.	34.3	33.9	32.8	31.4	30.3	30.8	29.6	29.8	29.1	28.9	29.0	28.8	28.8	28.0
	Max.	35.0	34.9	34.4	34.6	32.1	32.0	31.8	31.3	31.6	31.5	31.2	31.0	31.2	30.4

of life are summarized in Table 3 and graphically presented in Figs. 2 to 5.

An initial drop in peripheral temperatures (heel and palm) occurred during the first 30 minutes of life. Thereafter the temperatures in these skin areas became stabilized but remained at low levels during the first four hours, when infants were kept at a room temperature of 24 to 26 with adequate clothing. At 24 hours of age all infants maintained a steady skin temperature averaging from 30 to 31.6 C. The room temperature of the nursery was also maintained at 24 to 26°C.

Soon after birth and during the first 4 hours of life the early clamped infants had a significantly lower skin temperature in the heel and palm than the late clamped infants (Table 3).

Five to ten minutes after birth, the earlobe skin temperatures were already noted to be lower than the intrauterine

During the first 4 hours of age the infants were kept in an observation room where the temperature varied between 24 and 26°C The infants were placed in bassinets during the first hour and were covered with one cotton sheet and one woolen blanket Between one and 2 hours, the infants were briefly washed with warm water weighed and measured for their head circumference and body length and were then clothed with one cotton dress, a cotton diaper and again covered by a cotton sheet and a woolen blanket. These routine procedures usually lasted for 15 to 20 minutes. The extremities of the infants were enclosed in the sheet and blanket.

At 5 to 10, 15, 45 and 60 minutes of age the rectal temperatures were taken using a conventional thermometer inserted 3 cm deep into the rectum, skin temperatures on the center of both heels, epigastrium, the center of both palms and the anterior surface of both earlobes were taken with an electrical thermometer type TE 3 (Ellab Instrument Copenhagen) using the type H 1 skin applicator The response time of this electrode was 1 to 3 seconds. During each measurement the skin applicator was applied on the areas to be measured for 3 to 5 seconds and the readings recorded when it became stable An average of two readings was obtained on each side in the case of heels, palms and earlobes. In the case of earlobes the reading of the side on which the infants head was lying was usually higher than that of the exposed side; but during the first 4 hours of life the difference of paired readings did not exceed 0.5°C and comparison of the readings of the exposed sides alone to the average readings of both earlobes revealed no significant difference The rectal and skin temperature readings were repeated at 2, 4, 24, 48, 72, 96 and 120 hours of age Additional rectal temperature measurements were made at 5 and 6 hours of age. The measurements during the first hour of age were made at variable times of the day depending on the time of delivery while the daily readings were made between morning feeding schedules (between 9 a.m. and 1 p.m.)

No other procedures were done on these infants except for a scalp venipuncture at ½ hour of age to determine venous hematocrits. The hematocrits were measured by the microtechnique described by Guest and Siler [11]

In a separate experiment, the skin temperature of 6 infants whose cords were clamped late was measured from birth through 15 minutes of age. When "crowning began, the temperature of the scalp was measured when it appeared in the vulva during each uterine contraction. When the infant was delivered, the heels and palms were wiped dry with gauze and skin temperatures were measured at 0, 15, 30, 45, 60 seconds and every minute thereafter until the 15th minute after birth.

Results

There was no significant difference in the sex distribution birth weight and duration of labor between early and late clamped infants. At ½ hour of age, the early clamped infants had significantly lower hematocrit values than the late clamped infants (Table 1) This is ascribed to a higher blood volume in the latter group of infants, as had been demonstrated previously [27]

In six infants whose skin temperatures were continuously recorded from birth through 15 minutes of life (Fig 1 Table *) the heel and palmar skin temperatures averaged 35 4 C at birth and this was followed by a steep drop of 6°C within the first 15 minutes of extra uterine life

The scalp temperature averaged 34 8°C a few minutes before birth it fell by 2.6°C at 5 minutes but rose by 1 C during the next 10 minutes.

The serially measured skin temperatures of 16 late and 14 early clamped infants from 5 to 10 minutes through the 5th day

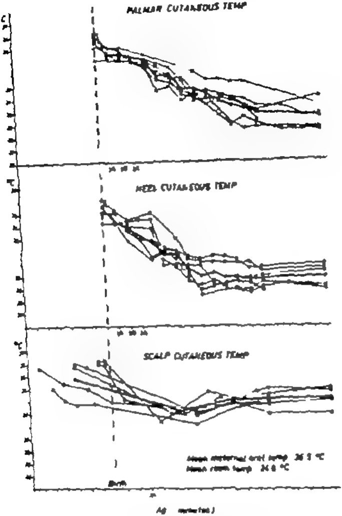


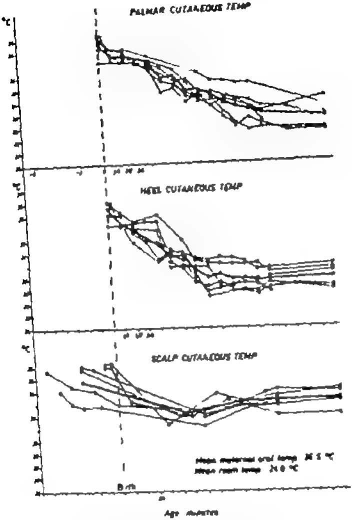
Fig. 1 Palmar heel and scalp cutaneous temperature changes in 6 newborn infants from birth through 15 minutes of age. Each line connects consecutive readings of each infant, and the heavy lines represent the mean values.

temperature environment. The early clamped infants had a mean temperature of 31.5°C while the late clamped infants, of 32°C. *Unlike the heel and palm tempera*tures which revealed an initial drop the earlobe temperatures showed a gradual rise during the first 4 hours of life. Scalp temperatures were not studied beyond 15 minutes of age however it is quite likely that the skin temperature changes of the scalp parallel those of the earlobes. *Unlike the heel* and palmar areas, only a slight difference in earlobe temperatures was observed between the early and late clamped infants: *the early clamped infants* had lower earlobe temperatures than the

TABLE 3 *Skin temperatures in the heels palms and earlobes of 30 newborn infants with early and late cord clamping at birth*

SEM – Standard error of the means; N – number of observations.

Skin areas	Group		Age: 5–10 Minutes	15	30	45	1 Hours	2	4	24	48	72	96	120
Heels	Late clamped	Mean	31.7	30	29.5	29.4	30.0	29.0	29.4	30.8	31.6	29.2	30.0	29.6
		SEM	0.54	0.64	0.43	0.45	0.39	0.30	0.35	0.30	0.43	0.81	0.57	0.09
		N	6	14	15	14	12	9	10	16	1	10	11	8
	Early lamped	Mean	30.0	29.0	28.2	28.2	28.6	27.9	27.7	30.0	30.6	29.7	30.0	29.8
		SEM	0.46	0.33	0.38	0.33	0.36	0.35	0.19	0.40	0.50	0.27	0.73	0.54
		N	5	13	12	11	11	6	10	14	10	10	5	5
	t		2.39	2.11	3.09	2.14	–.26	2.39	4.25	1.26	1.54	0.71	0	0.24
	p		< 0.05 > 0.025	> 0.05 > 0.025	0.003	< 0.05 > 0.025	< 0.05 > 0.025	< 0.05 > 0.025	< 0.001	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Palms	Late clamped	Mean	31.1	30.1	29.4	29.0	29.0	28.1	29.3	31.6	31.5	30.6	3..1	31.4
		SEM	0.22	0.26	0.26	0.28	0.28	0.35	0.60	0.27	0.48	0.50	0.60	0.72
		N	6	14	14	14	12	11	9	16	12	9	11	8
	Early clamped	Mean	31.1	28.9	28.4	28.1	28.1	27.7	28.0	30.7	31.2	30.5	30.3	30.7
		SEM	0.63	0.29	0.23	0.33	0.30	0.37	0.28	0.14	0.58	0.33	0.71	0.41
		N	5	12	12	10	9	6	9	13	10	10	5	5
	t		0	3.07	2.38	09	–.[illegible]0	0.8	–.10	2.9	0.40	0.17	1.93	0.07
	p		> 0.05	< 0.005	0.025	< 0.05 > 0.025	< 0.05 > 0.025	> 0.05	< 0.05 > 0.025	< 0.010	> 0.05	> 0.05	> 0.05	> 0.05
Earlobes	Late clamped	Mean	32.0	32.0	32.2	32.2	[illegible]	[illegible]	33.0	34.4	34.1	33.6	33.4	33.9
		SEM	0.62	0.33	0.27	0.38	0.25	0..7	0.53	0.23	0.20	0.43	0.43	0.29
		N	6	14	[illegible]	14	12	11	8	16	1	10	[illegible]	8
	Early clamped	Mean	31.5	30.9	31.5	31.7	31.5	31.3	32.4	33.3	34.1	34.1	33.2	33.7
		SEM	0.49	0.21	0.47	0.40	0.44	0.79	0.04	0.30	0.32	0.18	0.34	0.20
		N	5	12	12	10	8	6	9	13	9	11	5	5
	t		0.63	2.75	0.94	1.0	2.7	1.44	0.73	2.55	0	1.05	0.37	0.57
	p		> 0.05	< 0.025	> 0.05	> 0.05	< 0.025	> 0.05	> 0.05	< 0.025	> 0.05	> 0.05	> 0.05	> 0.05



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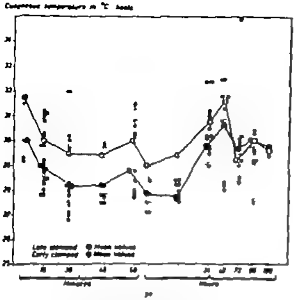


Fig 2. Heel cutaneous temperatures in 16 late clamped and 14 early lamped infants from birth thro gh 5th day of lif

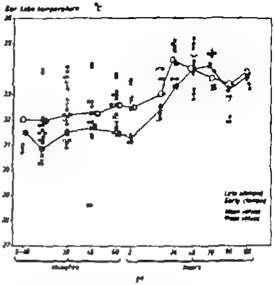


Fig. 4 Earlobe cutaneous temperatures in 30 newborn infants with early and late clamping of the cords, during the first 5 days of life.

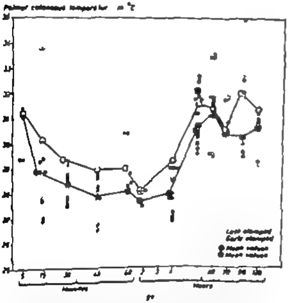


Fig 3. Palmar cutaneous temperatures in 30 newborn infants during the first 5 days of lif 14 infants belonged to the early clamped and 16 to the late clamped group.

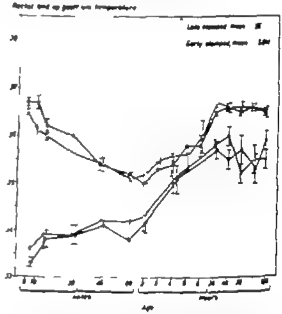


Fig. 5. Rectal and epigastric skin temperature in 30 newborn infants with early and late cord clamping during the first 5 days of life. The uppe two curves represent rectal temperature while the l we two curves represent pigastric cutaneous temperature.

late clamped infants at 15 minutes 4 and 24 hours of age.

The rectal and epigastric temperature curves of the early and of the late clamped infants are shown in Fig 5 The rectal temperatures at birth averaged 36 7°C in the early clamped infants and 36.5°C in the late clamped infants, and both

groups showed an initial fall during the first t o hours, followed by a gradual rise in the third hour and reaching stable levels at the 4th hour of life. The skin temperature on the epigastrium of the early clamped infants immediately after birth averaged 33.6°C while that of the late clamped infants 33.3°C. A gradual rise thereafter ensued, the temperatures reaching 35.7°C and 35.8°C at 4 hours of age in early and late clamped infants, respectively with no significant difference between the two groups (Fig 5).

Comments

The peripheral skin temperatures of newborn infants drops precipitously immediately after birth, probably as a result of sudden exposure of the neonate to a cold environment, since these infants are transferred within seconds from an intra uterine temperature environment to the delivery room with a temperature of 4°C. The effect of this abrupt postnatal change in thermal environment (during the process of delivery) upon the initial circulatory and respiratory changes following birth was not the object of this investigation However it seems pertinent to mention that this environmental change may play an *important role in the initiation of* the first breath.

It is of interest that the skin temperature of the earlobes did not exhibit the fall noted in the skin of the palms and heels during the first hours of life. This is perhaps related to the anatomy of the cutaneous blood vessels of the earlobes which differ from those elsewhere in the body in that arterio-venous shunting is abundant as shown in animal experiments [12]. This anatomical peculiarity could also explain the smaller difference in earlobe cutaneous temperature between early and late clamped infants which may be due to greater individual variations.

The rectal temperature changes observed in this study during the first 5 days of life are in agreement with the results of other workers [7 15, 25] No significant difference was found in epigastric and rectal temperatures between the early and late clamped infants during the first 5 days of life. *The low rectal temperatures during the first few hours of life have been attributed by Bruck [3] to Immaturity of the* infant s thermoregulatory mechanism" *Recent works have shown that chemical* thermogenesis in the newborn infant depends largely on noradrenaline [13 16 24]. When the newborn infant is exposed to a cold environment, it promptly responds with increased heat production, by augmenting brown fat metabolism, and with reduction of heat loss by peripheral vasoconstriction, both mediated by nor adrenaline The persistently low rectal temperatures during the first 4 hours of life suggest that for some as yet unknown reason chemothermogenesis was not adequately achieved

In this study the factors which might *affect the infants* skin temperature such as the amount of clothing, room tempera ture [23], *body weight [8] and the clinical* condition of the infants [14] were relatively similar in both groups *of infants. The* significantly lower skin temperatures of early clamped infants, particularly in the palms and heels, could be explained by a comparatively smaller skin blood flow in these subjects This, in turn, may be due to their smaller blood volume and greater

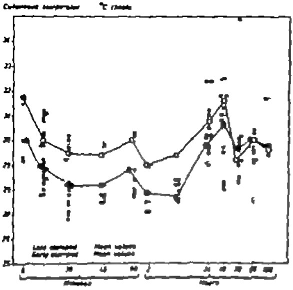


Fig 2 Heel cutaneous temperatures in 16 late clamped and 14 early clamped infants from birth through 5th day of life

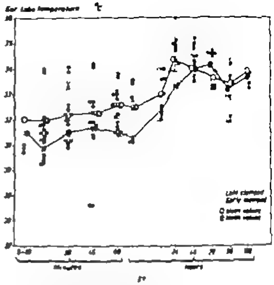


Fig. 4. Earlobe cutaneous temperatures in 30 newborn infants with early and late clamping of the cords, during the first 5 days of life.

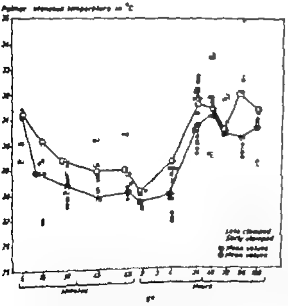


Fig 3. Palmar cutaneous temperatures in 30 newborn infants during the first 5 days of life. 14 infants belonged t the early clamped and 16 to the late clamped group.

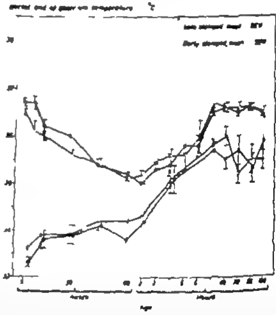


Fig 5. Rectal and epigastric skin temperatures in 30 newborn infants with early and late cord clamping during the first 5 days of life. The upper two curves represent rectal temperature while the lowe two curves represent epigastric cutaneous temperature

late clamped infants at 15 minutes, 4 and 24 hours of age

The rectal and epigastric temperature curves of the early and of the late clamped infants are shown in Fig 5 The rectal temperatures at birth averaged 36.7°C in the early clamped infants and 36.5°C in the late clamped infants and both

groups showed an initial fall during the first two hours, followed by a gradual rise at the third hour and reaching stable levels at the 4th hour of life. The skin temperature on the epigastrium of the early clamped infants immediately after birth averaged [illegible] 6°C while that of the late clamped infants 33.3°C. A gradual rise thereafter ensued the temperatures reaching 35.7°C and 35.8°C at 24 hours of age in early and late clamped infants, respectively with no significant difference between the two groups (Fig. 5)

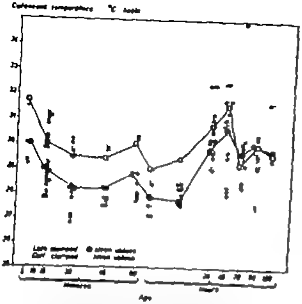
Comments

The peripheral skin temperatures of newborn infants drops precipitously immediately after birth, probably as a result of sudden exposure of the neonate to a cold environment, since these infants are transferred within seconds from an int a uterine temperature environment to the delivery room with a temperature of 24°C. The effect of this abrupt postnatal change in thermal environment (during the process of delivery) upon the initial circulatory and respiratory changes following birth was not the object of this investigation. H wever it seems pertinent to mention that this environmental change may play an important role in the initiation of the first breath

It is of interest that the skin temperature of the earlobes did not exhibit the fall noted in the skin of the palms and heels during the first hours of life This is perhaps related t the anatomy of the cutaneous blood vessels of the earlobes which differ from those elsewhere in the body in that arterio-venous shunting is abundant as shown in animal experiments [12] This anatomical peculiarity could also explain the smaller difference in earlobe cutaneous temperature between early and late clamped infants which may be due to greater individual variations.

The rectal temperature changes observed in this study during the first 5 days of life are in agreement with the results of other workers [7 18 25]. No significant difference was found in epigastric and rectal temperatures between the early and late clamped infants during the first 5 days of life. The low rectal temperatures during the first few hours of life have been attributed by Bruck [3] to immaturity of the infant s thermoregulatory mechanism Recent works have shown that chemical thermogenesis in the newborn infant depends largely on noradrenaline [13 16 4]. When the newborn infant is exposed to a cold environment, it promptly responds with increased heat production, by augmenting brown f t metabolism, and w th reduction of heat loss by peripheral vasoconstriction, both mediated by noradrenaline. The persistently low rectal temperatures during the first 4 hours of life suggest that for some as yet unknown reason, chemothermogenesis was not adequately achieved.

In this study the factors which might affect the infants skin temperature such as the amount of clothing room temperature [23] body weight [8] and the clinical condition of the infants [14] were relatively similar in both groups of infants. The significantly lower skin temperatures of early clamped infants, particularly in the palms and heels, could be explained by a comparatively smaller skin blood flow in these subjects. This, in turn, may be due to their smaller blood volume and greater



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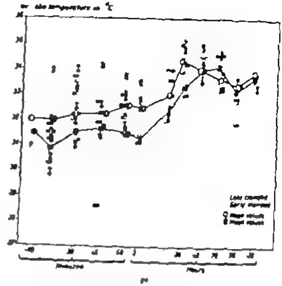

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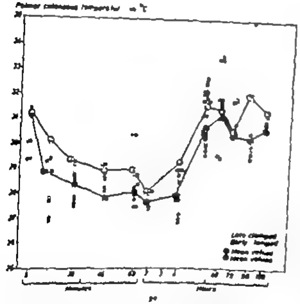

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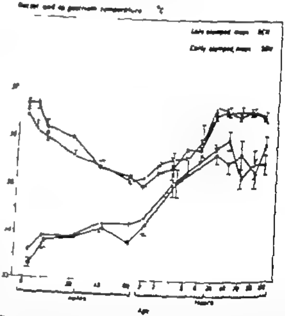

Fig 5 Rectal and epigastric skin temperatures in 30 newborn infants with early and late cord clamping during the first 5 days of life. The upper two curves represent rectal temperature whil the lowe two curves represent epigastric cutaneous temperature

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The rectal and epigastric temperature curves of the early and of the late clamped infants are shown in Fig 5 The rectal temperatures at birth averaged 36 7°C in the early clamped infants and 36.5°C in the late clamped infants and both

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cutaneous vasoconstriction. It has been suggested that the newborn infants possess an intact vasomotor reflex pathway as early as their first day of life [17 22]. Although cutaneous temperature does not always reflect skin blood flow variation [6 10] it is generally agreed that within certain limits, the two are positively correlated [2]. Variations in regional skin blood flow have not been investigated obviously because of technical difficulties, although it seems logical to assume that they exist particularly in areas exposed to different thermal environments. Varying degrees of regional vasoconstriction may be an important factor in this situation. This may perhaps explain the higher skin temperatures in the unexposed epigastric area as compared to those of the hands and feet, and the similarity of the epigastric skin temperatures of the EC and LC subjects in this study.

Summary

Temperatures of the rectum skin areas of the heels, palms, earlobes and epigastrium were serially measured in 36 normal full term newborn infants from birth through the 5th day of life. The umbilical cords of 14 infants were clamped immediately after birth while in 22 infants the cords were tied after arterial pulsation had stopped. At birth the mean skin temperatures of heels and palms dropped precipitously from 35.4 C to 29.8°C during the first 10 minutes of life. The heel and palm temperatures showed a further decline during the first 4 hours of age while the earlobe and epigastrium temperatures gradually increased at the same time.

The early clamped infants had a significantly lower skin temperature at the palms, heels and to a lesser extent at the earlobes. This is considered as indirect evidence of lower peripheral skin blood flow in this group of infants. No difference was observed in the cutaneous epigastric and rectal temperatures between the two groups.

Acknowledgement

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Table 1 *Nomenclature of human immunoglobulins*

W.H.O. adopted nomenclature (Class of Immunoglobulin)	Synonyms
γG (Ig G)	γ₂, γ-globulin, γss, 7S γ globulin
γM (Ig M)	γ-1M, β-2M, γ macroglobulin, 19S γ globulin
γA (Ig A)	γ-1A, β-2A, 7S γ-1
γD (Ig D)	None

if not all appears to be of fetal origin [41, 45].

Until only a few years ago hypo- or agammaglobulinemia could be demonstrated by paper electrophoresis only when the total gamma-globulin was markedly reduced or absent. To-day by immunoelectrophoresis and other refined methods, it is possible to identify and to measure precisely the various Ig fractions and to correlate their absence with specific immunologic defects.

It is well established that patients with severe hypogammaglobulinemia are highly susceptible to bacterial infection and that they fare very poorly when they are affected by bacterial infection, their immunological behaviour to viruses is normal, although they are uncapable of forming antiviral antibodies. These patients are not susceptible to reinfection upon exposure to viruses with which they had been previously infected. Tuberculosis runs a normal course in these individuals [19] and the addition of phytohemagglutinin (PHA) to cultures of their peripheral blood produces a normal lymphocytic response. However, cultured lymphocytes do not stain with fluorescent antigamma globulin, nor do they incorporate radioactive aminoacids into gamma-globulin [22]. All these indicate that individuals with agammaglobulinemia, although lacking the ability to develop humoral resistance, are capable of developing cellular resistance.

In 1950 Glanzman and Riniker described two babies with the clinical and pathological findings of a syndrome which they

Table 2. *Biological and biophysical properties of immunoglobulins (from Smith R.T. [41] slightly modified)*

Property	γG	γA	γM
Molecular weight	155,000	160–500,000	900,000
Sedimentation rate	6.7 S	6.5–9 S	17–20 S
Opsonizing properties		?	+ + + +
Bactericidal effects	+	?	+ + + +
Toxin neutralization	+ + +	0	0
Complement fixation	+ +	?	?
Half-life in serum	23 days	6 days	5 days
Primary distribution	Extracellular fluid (40 % in intravascular pool)	Secretions of breast, salivary, respiratory in testinal epithelium (40 % in intravascular pool)	Intravascular (80 % in intravascular pool)
Placental transport	+	0	0

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From the Pediatric Clinic of Athens University

Dangers of Immunization in Immunologically Incompetent Individuals

by N MATSANIOTIS

For a long time immunity has been conveniently divided into two components, humoral and cellular The first is represented by the immunoglobulins, the products of antibody forming cells the second is strictly associated with the lymphocyte and is mainly expressed as delayed hypersensitivity This distinguishing of immunity with increasing knowledge becomes more and more vague and in a few years it may seem obsolete However for purposes of better understanding this distinction cannot be discarded for the time being

Since Bruton s first description of congenital agammaglobulinemia some 15 years ago much progress has been made towards a better understanding of the multifold nature of the human immune response

The tremendous evolution of the basic sciences provided the means to investigate the human immune response in detail It was shown for example that each specific gamma globulin antibody differs in structure from all other gamma-globulins having a different antibody specificity in other words that a specific antibody activity depends upon the chemical structure of the immunoglobulin molecule [10 11]

The nomenclature of human immunoglobulins adopted in 1964 at the meeting of WHO in Geneva [8] is shown in Table 1 It is wise to use these terms in order to avoid confusion in a field which is progressing so rapidly

In Table 2 the main biological and biophysical properties of the immunoglobulins (Igs) have been summarized.

Recent work by van Furth and his colleagues [44] indicates that the fetus and the newborn, both premature and full term, are to some degree capable of forming IgG and IgM. Synthesis of significant amounts of IgG begins at one month of age reaching adult levels at the age of two years. Following appropriate antigenic stimulation IgG appears in the serum right after IgM.

IgA is mainly produced by plasma cells lying in large numbers in the subepithelial layer of mucous membranes. They are secreted actively by the acinar and the epithelial cells of the salivary glands, as well as by the glands of the respiratory and gastrointestinal tracts Serum IgA probably represents transport IgA These Igs are not produced by the fetus nor do they cross the placenta

In the newborn the serum IgM level is only 1/10th of the adult level [44] Most

TABLE 3. *Immunologic deficiency states (from Fireman P., Johnson H. A. and Gitlin D. [14], slightly modified)*

Immunologic deficiency states	γG	γA	γM
I. In the presence of adequate numbers of small lymphocytes			
1. Agammaglobulinemia (Bruton)	–		±
2. Dysgammaglobulinemia type 1			
3. Dysgammaglobulinemia type 2			
4. Dysgammaglobulinemia not yet described			
5. Dysgammaglobulinemia not named			–
6. Dysgammaglobulinemia not named			
II. In the presence of thymic alymphoplasia with lymphopenia			
1. Common type			
2. Nezelof et al., Fulginiti et al.			
3. Fireman, Johnson and Gitlin			+
4. DiGeorge et al.			
Ataxia Telangiectasia		–	
Normal Individual			

with thymic alymphoplasia but normal Ig levels. There is considerable evidence that the thymus not only supplies peripheral lymphoid organs with immunologically competent cells, but also elaborates through its reticular epithelial cells a factor(s) necessary for the normal immunologic development of exothymic lymphocytes [24]. The presence of a dysplastic thymus implies a defect in a very early stage of the evolution of the immune mechanism. This may involve, to a different degree both the development of the thymus, and hence the immunologic competence of the circulating lymphocyte, and the biochemical maturation of the plasma cell which may elaborate normal amounts of immunologically inefficient gamma-globulin. This, of course, is merely a hypothesis which must await proof, but it appears to fit very well with the expression of immunologic deficiency in these patients.

The various immunologic deficiencies have been summarized in table 3. Patients with the pure Bruton type of agammaglobulinemia do not appear to be at risk, if vaccinated with vaccines containing toxoid, killed bacteria or even living attenuated bacteria [17]. Since they are unable to produce detectable antibody their only danger following diphtheria or tetanus toxoid vaccination, for example, lies with the fact that they have acquired no immunity at all, in spite of their vaccination.

Most if not all BCG vaccinated agammaglobulinemic children develop tuberculin hypersensitivity and acquired resistance to tuberculosis [19]. Furthermore, with few exceptions these children have been vaccinated against smallpox with no untoward reaction. Both primary takes and accelerated reactions have been observed and, although antibodies do not appear in the serum following vaccination, these chil-

termed essential lymphocytophthisis [18] Many more cases have been described since under the terms of congenital agammaglobulinemia with lymphopenia thymic alymphoplasia or alymphocytosis, familial lymphopenia or the Swiss type of agammaglobulinemia. The salient features of this syndrome which constitutes the second major class of immunologic incompetence are (a) a downhill clinical course leading to death within the first two years of life, (b) agammaglobulinemia (c) a lymphocyte count which is usually though not invariably low (d) inability to develop delayed hypersensitivity and/or to reject homografts and (e) aplasia or severe hypoplasia of the thymus gland and of the entire peripheral lymphoid system Thymic alymphoplasia is mainly transmitted as an autosomal recessive characteristic but there is evidence that it may be transmitted as an X linked characteristic [38] Peripheral lymphocytes from patients with thymic alymphoplasia cultivated with PHA fail to multiply and/or differentiate [28] In short, these individuals in addition to their inability to produce antibody are incapable of developing delayed hypersensitivity they are incompetent in both humoral and cellular resistance It should be pointed out however that patients have been described with proved thymic alymphoplasia in whom the values of all Igs were normal, [9 15 33] one patient had a normal number of plasma cells normal IgM but no IgG or IgA [14].

These patients form a third class of immunologic incompetence they do not develop delayed hypersensitivity or reject homografts which implies that their lymphocytes are immunologically incompetent, they are deprived of the ability to develop cellular resistance although they do possess plasma cells and may produce sufficient amounts of all or some Igs.

Another variant of immunologic incompetence associated with dysplasia of the thymus gland is that described in patients with ataxia telangiectasia or the Louis-Bar syndrome [13 35] These patients have no IgA but their IgG and IgM are normal or nearly normal In some cases more pronounced hypogammaglobulinemia or even agammaglobulinemia has been revealed by paper electrophoresis. Autopsy findings are variable—actually no more than 10 or 15 cases have been autopsied until now In most instances the thymus was dysplastic with few if any Hassal's corpuscles. The entire lymphoid tissue was poorly developed with few and small lymph follicles. Most of these patients died before they reached adult life following severe infection. The absence of IgA does not appear to account—at least mainly—for susceptibility to infection in these patients A broad spectrum of immunological deficiencies both humoral and cellular would appear to offer a more plausible explanation for their proneness to infection. Cellular immunity may be incomplete as shown in two patients who rejected skin homografts poorly and developed a sluggish hypersensitivity reaction. Interestingly these two patients, although possessing normal amounts of IgG and IgM, developed an incomplete antibody response when challenged with diphtheria tetanus pertussis or typhoid antigens and they developed no antibody response to viral antigens [30]

This form of immunologic incompetence associated with ataxia telangiectasia may be in a way similar to that in patients

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dren develop delayed hypersensitivity to heat-killed vaccinia virus [17]

BCG vaccination is a very safe procedure and millions have been inoculated. However there are 9 cases described in the literature [1 2 3 4 6 12 16 24 32 43 45] who died of generalized BCG infection in most instances a few months after vaccination. Some authors who reported such cases thought they were associated with the agammaglobulinemia observed in their patients. Others attributed death to some obscure inherent or acquired impairment of the host's immunologic response However no satisfactory explanation had been offered for these fatalities until very recently Matsaniotis and Economou Mavrou reinvestigated the case histories of all patients reported to have died of generalized BCG infection [29 30] The following case report by Bouton *et al* is illustrative [3]:

This was a boy the first child of healthy parents. He had been BCG vaccinated at birth and was admitted to hospital at the age of six months because a swelling had appeared in the left axilla five days previously The lesion at the site of vaccination had developed when he was six weeks old and was still discharging The abscess was incised, a lot of green pus was evacuated but no organisms were cultured by routine methods. The patient was readmitted at the age of 9 months because his BCG ulcer and axillary sinus were still discharging A chest X ray showed diffuse miliary shadowing throughout both lungs.

His white cell count was 9 000/cmm with only 7% lymphocytes (630/cmm) His gamma-globulin was very low (0 21 g/100 ml) His Mantoux reaction was negative up to 1 100 u of O T Plasma cells could not be found in the bone marrow A second gamma-globulin determination gave 20 mg/100 ml In spite of antituberculous and gamma-globulin therapy the patient died on the day of admission.

At autopsy the tonsils were very hypoplastic. There were no adenoid and no carinal lymph nodes. Miliary nodules were found scattered throughout the lungs, the spleen and the left adrenal. In the mesentery small lymph nodes were found

On microscopic examination the miliary nodules consisted almost entirely of epitheloid cells. There was no necrosis, caseation or cuffing by lymphocytes. Numerous BCG were found in the center of these nodules. The lungs showed the characteristic picture of pneumocystis carinii pneumonia. At the site of vaccination there was no caseation and hardly any cellular reaction except by macrophages. The axillary lymph nodes contained no lymphocytes. Lymphoid tissue was not found in the tonsils and the adenoids.

The remaining BCG fatalities were very similar Table 4 shows that, apart from two cases where the patients were 7 and 19 years old respectively at the time of vaccination, the patients were vaccinated as newborns or within the first 6 weeks of life and died as infants There were 5 males and 4 females With the exception of case 6 which will be discussed later all patients in whom pertinent information is available had profound peripheral lymphopenia—less than 2000/cmm and in about one half of the counts less than 1000/cmm The skin reaction to 100 u of O T was invariably negative showing that these patients were all uncapable of developing delayed hypersensitivity In three of the six babies the serum gamma globulins were absent or very low and in case 3 plasma cells were completely absent, which is indirect evidence that this baby also had hypo- or agammaglobulinemia. We do not know what the gammaglobulins were in case 1 and case 4 is the only case

Table 4. Main clinical laboratory and histopathological features of BCG fatalities

Author	Sex and age at vaccination	Age at death	Peripheral lymphocytes (per mm)	Skin reaction to 100 u OT	Tubercles	Serum gamma globulins
1. Hallström & Hård, Sweden, 1953	♀ days	15 months	?	(−)	( )	?
2. Falkmer et al., Sweden, 1953	♂ 4 day	9 months	1620	( )	Only at site of vaccinat. and spleen	( )
3. Chaed & Zacchia, Austria, 1958	♀ 4 days	6 months	?	( )	( )	λ plasma cells
4. Arana et al. Chile, 1960	♀ 9 days	5 months	418 1760	( )	( )	(+)
5. Bruun et al., G. Britain, 1963	♂ 4 days	9 months	630	( )	( )	(−)
6. Gerdberg et al., Norway 1963	♀ 6 weeks	7 months	2348	( )	( )	(−)?
7. Meyer & Jensen, Denmark, 1964	♂ 7 years	9 years	667 691 1020 1972 630 2440 596	(−)	( )	(+)
8. Thrap-Meyer et al., Norway 1964	♂ 10 years	24 years	938 1690 2372	( )	( )	(+)
9. Carlgren et al. Sweden, 1965	♂ Newborn	9 months	1000–2500	( )	( )	(−)

with normal gamma-globulin levels. With the exception of case 2 in whom tubercles were detected at the site of vaccination and in the spleen, tubercles were not found in any of these cases.

Case 3 deserves special consideration. There is strong evidence that the family of this girl was affected by an inborn immunologic defect. Three of the four children died as infants, two of sepsis presumably one of generalized BCG infection. Nevertheless, this girl was the only BCG fatality who had no lesion at the site of vaccination and no regional complication. She was definitely not lymphopenic; she had specific granulation tissue but little if any tendency to tuberculoid structure and only faint cellular reaction. Another point deserving consideration is that in the course of two months her gamma-globulins are reported to have been absent, normal and very much decreased on three separate occasions.

Two more BCG fatalities have been described while this review was being prepared [26 44a] In both the thymus was extremely hypoplastic

The cardinal points in each of the BCG fatalities with the exception of case II were firstly the absence of tuberculin hypersensitivity secondly profound peripheral lymphopenia and thirdly inability to form tubercles. It is well established that in a very small minority of BCG vaccinated children a positive tuberculin reaction fails to develop These children, however develop increased resistance to tuberculosis, they are capable not only of forming tubercles but also of developing immunocytes in numbers which are closely comparable to those of children with a positive tuberculin reaction following BCG vaccination [7] Their lymphocytes respond to antigenic stimulation with tuberculin in in vitro cultures by proliferation and differentiation [7]

The tubercle is a typical defensive cellular structure In human beings it takes about four weeks for tubercles to be formed and for tuberculin hypersensitivity to develop in response to the penetration of the mycobacterium By this time the in vitro lymphocytic response to tuberculin—presumably reflecting the lymphocytes which become immunocytes specifically oriented against the mycobacterium and tuberculin—is maximal [27] On becoming an immunocyte the lymphocyte acquires immunologic memory It multiplies and differentiates under appropriate antigenic stimulation and this results in the rapid production of the same type of cells and in the acceleration of all phases of the chronic inflammatory infiltrate There are more cells and they accumulate more rapidly thus meeting the requirements of the general biological phenomenon of defense in a quicker and therefore better way This, in fact, is the only specific effect of antigen upon immunocytes which has been demonstrated conclusively [40] and actually it is the essence of cellular immunity

Very little is known of the factor(s) causing certain mononuclear phagocytes to cluster together as a nodular tubercle but it is rational to assume that under stimulation of antigen bearing cells, immunocytes which arrive at random agglomerate around these cells and begin to proliferate That immunocytes multiply locally is beyond reasonable doubt, for the tubercle continues to enlarge even after the blood supply to the area has been interrupted [30]

The foregoing discussion, together with the data collected from the BCG fatalities, strongly suggest that patients who died in infancy were all affected by congenital thymic alymphoplasia It is unfortunate that the thymus was examined at autopsy in only two cases [4 12] It was small, weighing respectively 1.5 and 6 g Its cortex was greatly reduced and the gland appeared to be composed largely of medullary tissue Hassal s corpuscles were almost completely absent We know nothing at all of the thymus in the remaining infants, but their inability to develop a positive tuberculin reaction or to form tubercles together with their persistent lymphopenia strongly suggest that had their thymus been examined its size and histology would have been characteristic of congenital thymic alymphoplasia [17].

The seven years old boy [32] and the young man [43 45] who died of general-

had BCG infection do not appear to fit into the syndrome of congenital thymic alymphoplasia. For one thing they both survived for a very long time: they must have been vaccinated against smallpox and most have contracted the common rural infections of childhood. How could their vaccination and their illnesses have been uneventful, if they were incapable of developing cellular resistance? Why then did they die of generalized BCG infection? Their primary lesion failed to heal, their tuberculin reaction did not convert, they were lymphopenic and incapable of forming tubercles. One possibility is that these two patients may have been affected by an acquired lymphopenic disorder. Waksman *et al.* [46] have shown that specific reduction in the number of peripheral lymphocytes in rats by means of antisera against lymphocytes can abolish the delayed hypersensitivity reaction against certain antigens. It would be very interesting to speculate whether a similar reduction of lymphocytes may occur in man as a result of anti-self reactivity. In any case, although the exact cause of fatal generalized BCG infection cannot be defined with certainty in these two cases, the evidence points to an immunologic disorder probably stemming from the thymus.

During the last 10 years, at least a dozen reports have been published describing death from progressive vaccinia in babies with agammaglobulinemia. Rosen and Janeway [37] reviewed these cases and pointed out that all cases in which pertinent information was given, infants dying from progressive vaccinia had profound lymphopenia. In one case it was noted at autopsy that the thymus was absent. They concluded therefore that these children all had thymic alymphoplasia to account for their deaths. Nevertheless, progressive vaccinia has also been observed in patients with Bruton-type hypogammaglobulinemia [15a].

Children with thymic alymphoplasia may be equally at risk if vaccinated with living attenuated viruses, such as the oral polio or the measles vaccine. To our knowledge there is only one case report of a boy who developed paralytic poliomyelitis 7 weeks after taking type 1 polio vaccine orally. This boy showed none of the features of thymic alymphoplasia. He was severely hypogammaglobulinemic and autopsy findings were consistent with those of Bruton's type of agammaglobulinemia [5].

Various attempts have been made to de novo institute immunological competence in patients with thymic alymphoplasia, thymic tissue and lymph nodes have been implanted, fetal liver cells, bone marrow and sensitized lymphocytes have all been given [23]. Neither of these procedures has been successful. And cases have been described with immunologic deficiencies in whom fatal aplastic anemia [21] or even pancytopenia [20] has developed following transfusion of viable leucocytes. These complications have been attributed to a graft-versus-host reaction, in other words to the effect of the transferred leucocytes which were accepted in the first place because of the host's immunologic incompetence [21].

The practical implications of this review are that although the safety of smallpox, BCG and oral polio vaccination cannot be contested, it should be recognized that in individuals with immunologic incompetence, especially of the cellular type, vac-

cination may be disastrous these individuals must be carefully sought for especially among the infant age group As a screening procedure infants with a history of repeated infection or persistent moniliasis should not be vaccinated with BCG smallpox or even oral polio vaccine until the diagnosis of thymic alymphoplasia can be excluded. This may be achieved by repeated counts of peripheral lymphocytes and, more safely by examination of lymphoid tissue obtained by rectal or lymph node biopsy

Disease may be an experiment of nature disease following vaccination is an experiment in which the participation of man is an overwhelming responsibility Every effort should be made to prevent death from procedures which are designed to prevent disease

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these discoveries which not only were of importance to medicine, but set the stage for the breathtaking developments of molecular biology of recent years.

Garrod's work was far ahead of his time His colleagues respected him his students loved him, his peers elected him to be the successor of Osler's prestigious chair at Oxford, but no one realized the general significance of his work. Even geneticists who should have known better ignored him and the literature on physiologic genetics of the 1920's and 1930's fails to mention him. Beadle's and Tatum's work which firmly established the one gene-one enzyme hypothesis was carried out in ignorance of Garrod's contribution.

Investigations on sickle hemoglobin

It took another discovery to establish biochemical genetics as a discipline of great relevance to medicine. In 1945, Pauling, the famous chemist, and Castle the renowned hematologist, served on a committee dealing with matters of national scientific policy Castle told Pauling that red cells from patients with sickle cell anemia when deoxygenated became sickled and showed birefringence in polarized light suggesting some type of unspecified molecular realignment Pauling later concluded that molecular abnormality of hemoglobin might best explain these phenomena and suggested to Harvey Itano, graduate student with medical degree, to investigate this problem. After much hard work and many negative findings, it became clear in 1949 that the electrophoretic mobility and, therefore the structure of hemoglobin of patients with sickle cell anemia was indeed different from that of normal hemoglobin. The somewhat puzzling genetic findings that parents of patients with sickle cell anemia were clinically well but had sickled red cells, was explained by finding both normal and abnormal hemoglobin in their blood [2]. Jim Neel's genetic conclusions (1949) [3] indicating that sickle cell anemia required the double dose of the sickling gene were confirmed by the biochemical data. Pauling realized the full general significance of these discoveries and pointed out that sickle cell anemia was the first example of a molecular disease.

The nature of the molecular abnormality in sickle cell anemia was not clarified until 1957 [4] Ingram a young biochemist, worked in the intellectually stimulating atmosphere of the Cambridge Laboratory of Molecular Biology Here, Sanger had established the amino acid sequence of insulin. Crick and Watson had demonstrated the double helix of DNA and Perutz and Kendrew were investigating the three-dimensional structure of hemoglobin and myoglobin. (By 1964 all these investigators had received Nobel prizes for their work) By digesting hemoglobin and separating the resultant peptides by various techniques, Ingram showed that the sickle hemoglobin molecule differed from that of normal hemoglobin by the substitution of only a single amino acid.

The stage was now set for a clear understanding of the nature of mutational alterations of protein molecules. Later work with bacterial tryptophane synthetase by Yanofsky and his group [5] confirmed what appeared evident when single amino acid alterations were found in many other abnormal hemoglobins. Amino acid alterations of the protein chain had a linear relationship to the mutational sites within

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Biochemical Genetics in Medicine[1]

by ARNO G MOTULSKY

Biochemical Genetics in Medicine

Origins of human biochemical genetics

Many advances in science have occurred by applying concepts and techniques from different disciplines to an unsolved problem Garrod a British physician, worked on various rare metabolic diseases such as alkaptonuria in the early part of this century He was struck by the familial nature of this disease and noted the increased frequency of first-cousin marriages among the nonaffected parents of his patients. Talking matters over with Bateson, the biologist who coined the term of genetics, these findings seemed best explained by the recently rediscovered Mendelian laws Thus, each parent of an alkaptonuric patient was assumed to be a latent or recessive carrier of the gene for alkaptonuria, having derived this gene from a common ancestor The double dose of a specific factor produced the disease rather than consanguinity by itself Under the influence of the physiologic chemist Fredric Gowland Hopkins and arguing from alkaptonuria pentosuria cystinuria and albinism Garrod concluded that normal metabolism was carried out by single discrete steps each probably under the control of specific hereditary factors. Blocks at some particular point of intermediate metabolism due to congenital deficiency of an enzyme would lead to excretion or accumulation of normal intermediates which ordinarily could not be detected. Garrod named disorders of this sort inborn errors of metabolism and ascribed a more general biologic significance to these diseases [1] He maintained that just as structure varied between individuals biochemical variability was likely He predicted that idiosyncrasies to drugs as well as various degrees of natural resistance against infections might be explained by the 'failure of members of a species to conform to an absolutely rigid standard of metabolism How happy Garrod would have been to learn that an enzyme deficiency of the red cell (G6PD deficiency) predisposes to hemolytic reactions by drugs and at the same time confers resistance against falciparum malaria! Garrod utilized concepts from biochemistry and genetics and applied them to human disease to found the field of biochemical genetics We can be proud that a physician—a true clinical investigator—made

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hemoglobin chains to the heme group. Hemoglobin is oxidized to methemoglobin at all times, but the physiologic reduction machinery of the red cell normally reduces the methemoglobin formed. The various types of Hb M resist reduction since the mutationally introduced tyrosine residues form a stable complex with the ferric ion of the heme group, so that methemoglobinemia and cyanosis result.

Polycythemia caused by an abnormal hemoglobin [9]. An abnormal hemoglobin was discovered in a family with mild polycythemia. Heterozygotes had clinical symptoms. This hemoglobin—Hb Chesapeake—was found to have an arginine→leucine substitution at the 92nd amino acid residue of the α chain, 5 amino acid residues away from the heme-linked histidine of the α chain. Hb Chesapeake showed a significantly increased oxygen affinity in red blood cells, as well as in the purified state which presumably explained the polycythemia. Neither methemoglobin nor increased blood destruction was found in Hb Chesapeake patients. Other cases of benign familial polycythemia may be caused by this type of abnormal hemoglobin.

Unstable hemoglobin diseases associated with hemolysis [10]. Occasionally an amino acid substitution may not grossly interfere with function, but may make the hemoglobin molecule more unstable. Blood destruction may follow. Several families with unexplained familial hemolytic anemia were found to have such unstable hemoglobins. In Hb Zurich the molecular site of substitution was identical to that in Hb M Saskatoon, the heme-linked histidine at the 63rd position of the β chain (his→arg). Patients with Hb Zürich are heterozygotes with chronic compensated hemolytic diseases. Affected patients develop severe hemolytic crises upon administration of a variety of oxidant drugs such as various sulfonamides. Severe methemoglobinemia occurs during the hemolytic crises, but is absent at other times.

Patients with Hb Seattle have chronic hemolytic diseases. The hemoglobin substitution affects position 70 or 76 of the β chain (ala→glu). Methemoglobin is not seen, but red cells from patients with Hb Seattle disease and Hb Zürich disease can be induced in vitro to form methemoglobin more readily than normal red cells. In both Hb Zürich and Hb Seattle the abnormal hemoglobin comprises more than 30% of the total hemoglobin. In a variety of other families with hemolytic anemia small amounts of highly unstable hemoglobins have been detected. The amount of these hemoglobins has comprised 10% or less. In several of these families many inclusion bodies have been detected particularly after splenectomy. The inclusion bodies may represent free α chains, such as has been detected in the hemolysates of patients with unstable β chain hemoglobin anomalies, such as Hb Köln, Hb Seattle and Hb St. Mary's. In another abnormal hemoglobin of this sort—Hb Ube-1—the investigators believed that the abnormality consisted of loss of reactivity of the sulfhydryl group at position 93 of the β chain.

Hb St. Mary's is associated with compensated hemolytic diseases. Although the specific site of the abnormality has not been identified yet, it is likely that the substitution affects the critical site of the hemoglobin molecule, since the absorption spectrum of Hb St. Mary's was abnormal.

the gene specifying the information for a given protein chain. Analysis of these chains could provide detailed information *regarding the site of mutation in the DNA* of the gene. Genes specifying the sequence of amino acids in protein chains were termed structural genes and the most common mutational alterations of protein were single amino acid substitutions.

Study with microorganisms yielded full understanding of the genetic code. Triplets of nucleotide bases contain information specifying which of the 20 amino acids is inserted into a protein chain and the composition of these DNA triplets has become recently clarified. All known amino acid substitutions in human hemoglobin can be explained by alterations of one of three nucleotide triplets which comprise the various coding units as worked out in microorganisms [6]. These findings conform to data on mutagenesis in lower forms of life and are of great biological importance in indicating that the genetic code is universal and applies to organisms as far apart as man and viruses.

Hemoglobin was found to be composed of four polypeptide chains. Two of the four hemoglobin chains were different and were described as the α and β chains. Each chain was found to be under control of a specific gene, the Hb α and Hb β genes. This finding has general significance for protein structure. Work with other proteins in recent years has shown that many proteins consist of several polypeptide chains and therefore require more than one gene for their *synthesis*. The one gene–one protein hypothesis has become the one gene–one polypeptide chain hypothesis.

Abnormal hemoglobins—A model of molecular disease [7]. Hemoglobin can be obtained freely from blood and many investigators all over the world initiated studies and surveys on hemoglobins. Within a few years it became clear that there was considerable biochemical variability of the hemoglobin molecule. Most hemoglobin variants were not associated with disease. If an amino acid substitution affects a portion of the molecule not involved in its physiologic function, i.e. oxygen carriage, altered electrophoretic mobility might result, but if the stability of the molecule is not otherwise impaired, the altered hemoglobin may carry out its usual function. However, a variety of hematologic diseases were found with amino acid substitutions near the critical functional site of the hemoglobin molecule, i.e., near the insertion of the heme group. These include positions 51–76 and 80–94 of the α chain and 57–76 and 85–96 of the β chain.

Hb M [8]. Chronic methemoglobinemia is one type of disease produced by amino acid substitution in the critical area of hemoglobin. Several abnormal hemoglobins producing methemoglobinemia and cyanosis exist. Clinical manifestations are observed in heterozygotes. Both α and β chain mutations producing Hb M have been found. In Hb M Boston and Hb M Iwate, histidine residues at the 58th and 87th positions of the α chain are changed to a tyrosine residue. An identical interchange has occurred at the 63rd position of the β chain to produce Hb M Saskatoon. Hb Milwaukee 1 is caused by a val→glu substitution at the 67th position of the β chain. It is noteworthy that positions 58 and 87 of the α chain and [redacted] of the β chain represent the points of attachment of the

hemoglobin chains to the heme group. Hemoglobin is oxidized to methemoglobin at all times, but the physiologic reduction machinery of the red cell normally reduces the methemoglobin formed. The various types of Hb M resist reduction since the mutationally introduced tyrosine residues form a stable complex with the ferric ion of the heme group, so that methemoglobinemia and cyanosis result.

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In Hb Köln, the abnormality was localized between the 83rd and 120th amino acid of the β chain [11]

The more unstable the abnormal hemoglobin the more difficult will it be to detect small quantities of the mutant hemoglobin in the blood. Heat instability has been seen in most of the unstable hemoglobins and may represent a good screening test for such disorders. Unfortunately this test will not be infallible since an innocuous hemoglobin abnormality—Hb Tacoma (β^{30} arg→serine) has also been associated with heat lability [12]

Sickle cell disease. The red cells of heterozygotes with sickle cell disease can be made to sickle *in vitro* but such carriers are quite well under most circumstances since more than 50% of their hemoglobin is of the adult normal type. With severe hypoxia such as at altitudes over 12 000 ft *in vivo* sickling may occur and splenic infarction may be observed. The unusual circulation of the kidney leads to hemoconcentration and relative hypoxia and may produce renal sickling and hematuria in the absence of structural renal abnormalities. Patients with homozygous sickle cell anemia have no normal adult hemoglobin and will exhibit *in vivo* sickling with resultant organ damage and chronic hemolytic disease The mechanism by which a substitution of a single amino acid produces severe deformities of red cell shape is believed to be stacking of sickle hemoglobin molecules [13]

Most other hemoglobin abnormalities have not produced any disease in the heterozygote state presumably because the mutants interfered with neither stability nor function of the hemoglobin molecule The reasons for blood destruction in patients homozygous for Hb C, Hb E and Hb D diseases are not yet apparent.

The thalassemias [14] In this group of diseases the genetic mutation leads to depressed synthesis of a given hemoglobin chain, i e α or β thalassemia, and causes reduction in the amount of hemoglobin in the red cells. Heterozygotes usually have only mild anemia but homozygotes may be severely affected. The genetic mechanisms causing suppression of the hemoglobin genes are largely unknown.

However one type of thalassemia could clearly be related to an unusual type of abnormal hemoglobin—Hb Lepore. This hemoglobin is a fusion gene product consisting of both δ and β hemoglobin chains. The δ chain is a physiologic gene product differs by only 9 amino acid substitutions from the β chain and forms the two non α chains of a minor normal hemoglobin. Hb A_2. The δ gene is closely linked to the β gene Nonhomologous crossing-over between the β and δ gene produces a deletion of a portion of the δ and β chains with formations of a hybrid $\delta\beta$ polypeptide. Hemoglobin synthesis of the hybrid $\delta\beta$ molecule proceeds at a reduced rate similar to that of the normal δ chain which only comprises 2% of the total hemoglobin and thalassemia results.

Since hemoglobin can be easily obtained and analyzed the correlation of structure and pathologic function has progressed further than for other genetic diseases. Certain generalizations can be made Variability of molecules is likely to exist for other proteins and enzymes Occasionally a molecular abnormality may be of selective advantage to its carriers and its frequency will become significant Since the

sickle cell trait confers resistance against falciparum malaria, the frequency of that trait is relatively high in areas of the world where this type of malaria was endemic, even though the homozygous state was relatively lethal. The selective advantage of other genetic traits is less well understood, although malaria is likely to explain the relatively high frequency of the thalassemias. When the active or critical site of molecule or its stability is affected, disorders of function may be expected, such as various anemias, polycythemia and methemoglobinemia in the case of the hemoglobin mutations. Physicians will see more of the disease-producing mutations. However if whole populations are screened, benign and harmless mutants will be more common.

Glucose-6-phosphate dehydrogenase deficiency of the red cell—A model for inborn errors of metabolism. Enzymes are proteins and the general lessons provided by hemoglobin disorders should apply to enzymatic abnormalities. Mutational effects might change the configuration of an enzyme and distort the active site of the enzyme or interfere with the stability of the enzyme. The active site might be directly affected. Cofactors might not be able to bind properly or subunit association or dissociation might be interfered with. Unfortunately the amount of enzyme which can be recovered for protein studies is very small, so that basic knowledge regarding the nature of the biochemical abnormalities is less advanced than that of abnormal hemoglobins. However enzyme deficiency has been demonstrated in many disorders already.

Red cell enzymes are more readily available than most other material and more detailed knowledge is available in this area. Abnormalities of G6PD are a good example. G6PD deficiency of the red cell is a heterogeneous disorder. Many different mutations may cause alterations in G6PD activity [15]. Some mutations change the electrophoretic mobility of the enzyme and do not cause enzyme deficiency. They are clinically asymptomatic. Others cause enzyme deficiency but are clinically harmless unless certain drugs or fava beans are administered and then hemolytic anemia develops. A different mutation causing G6PD deficiency exists among Mediterranean and African populations. The Mediterranean mutation produces a more severe type of enzyme deficiency with a wider spectrum of drug sensitivity than seen among Africans. Recent studies in our laboratory [15a] have helped to define the nature of the biochemical lesion in the African type of G6PD deficiency (A −). When red cells were fractionated by age it could be shown that very young cells from deficient subjects had almost identical enzyme activity as compared with normals. Enzymologic properties were normal. Serologic activity of mutant G6PD (A −) as assayed by neutralization of antibody prepared against purified normal G6PD also was normal. Column chromatography however showed structural differences when the A − mutant was compared with normal and with the electrophoretically identical mutant with normal enzyme activity (A +). These findings may be interpreted to indicate that a structural mutation leads to more rapid degradation of the enzyme during red cell ageing. Since the normal enzyme is a hexamer the process may well relate to increased subunit dissociation. In contrast, the Medi-

terranean type of mutation was shown to exhibit already diminished activity in young red cells and exhibited grossly altered serologic activity. Its abnormal kinetic properties as well as its chromatographic properties clearly establish this mutant as another structural abnormality.

Other *mutations* are associated with chronic hemolytic disease in the absence of any drug or food administration. Chemical studies have shown that even *in vitro* a highly unstable enzyme is found in patients of this type.

The relatively high frequency of G6PD enzyme deficiency in Africans and Mediterranean populations appears to be caused by a protective advantage against *falciparum* malaria [16]. The discovery of G6PD variations of the red cell illustrates that abnormality affecting a single enzyme explained diverse types of hemolytic anemias, such as hemolytic disease of the newborn, drug induced hemolytic anemia, food induced hemolytic anemia, hemolytic anemia by infection, and chronic *non* spherocytic hemolytic disease. Apart from G6PD deficiency other enzyme deficiencies affecting the red cell have been discovered to cause hemolytic anemia. These include pyruvic kinase deficiency, triose phosphate isomerase deficiency and hexokinase deficiency. *All of them* are inherited as autosomal recessive traits.

Control mutations in man! The discovery by Jacob & Monod [17] of a class of mutations in microorganisms causing interference with genetic regulatory elements rather than with structural enzyme protein has elicited much interest and was recently rewarded with a Nobel prize. If such mutations existed in man, one would expect severe enzyme or protein deficiency. Since regulatory mutations affect the function of linked structural genes, several related enzymes or proteins might be affected. The structure of the affected protein or enzyme would be normal. Increased rather than deficient enzyme activity also might be explained by controller mutations, although structural mutations at allosteric sites of an enzyme, making it less responsive to *inhibition* by small molecules, would be an alternative explanation. Many *inborn* errors in man have been ascribed to regulatory mutations but *none have* been proven yet. In several instances, where a regulatory mutation was postulated, more detailed study revealed a structural mutation such as in the African type of G6PD deficiency cited above. Increased pseudocholinesterase activity [18] *in a family* was shown to be associated with an electrophoretically demonstrable structural mutation rather than with a control mutation.

However, three diseases remain where a good case can be made for the existence of regulatory mutations. In one type of hereditary persistence of fetal hemoglobin (African type) there is complete suppression of the adult type β and δ hemoglobin chains which is fully compensated by fetal (γ) chain production. In another type (Greek) there is only partial suppression of β and δ chain production with smaller amounts of fetal (γ) chain synthesis. The African type could be explained by complete deletion of the adjacent β and δ genes. This explanation, however, is inadequate for the Greek type of this syndrome and an operator type of mutation suppressing the linked β and δ structure genes could well explain both conditions [14].

In orotic aciduria two enzymes, orotidylic pyrophosphorylase and orotidylic

decarboxylase, are depressed to 50% of their normal enzyme activity in the blood cells of heterozygotes. Since the two enzymes are closely linked in E. coli they might also be genetically linked in man and both be depressed by a control type of mutation [19].

In acute intermittent porphyria increased δ-amino levulinic synthetase activity has been demonstrated. A control type of mutation has been postulated [20], particularly since increased activity of this enzyme can be induced experimentally by the same drugs which precipitate the man disease in genetically predisposed riers. Structural studies on the human zyme, ho ever have not yet been car ed out, and a structural mutation is not led out.

Pharmacogenetics—Enzymatic variability as model for human susceptibility. Several xamples of genetic disorders which predispose to drug reactions have already een mentioned. Thus, Hb Zürich and 6PD deficiency of the red cell both redispose to drug induced hemolytic nemia.

It has become clear that some drug eactions and a good amount of variability in response to drugs may be caused by genetically determined biochemical differences bet een individuals [21]. Prolonged pnea following administration of succinylcholine is often caused by genetic alterations of *pseudocholinesterase,* the enzyme which normally inactivates succinylcholine. Several different mutants affecting pseudocholinesterase have been recognized. The most common type is found in 3–4% of the population, who are heterozygous for this trait, and represents a structural mutation of the pseudocholinesterase molecule. About 1/2,000 individuals are homozygotes. A rare mutation presents with no enzyme activity and is known as the silent allele. Heterogeneity again has been found in several cases presenting with no enzyme activity. In some cases, cross reactive material could be found. Sera with cross reactive material might represent examples of control mutations, but other explanations could also be offered for those findings. Individuals who are homozygous for the different pseudocholinesterase mutations, as well as mixed heterozygotes for two different mutations (such as those carrying the enzyme for the atypical common mutation, as well as for the silent mutation) were found to be drug sensitive. A simple screening test based on differential inhibition of the enzyme by enzyme inhibitors has been developed for use in agar gels [22] and has been extended for test tube use in our laboratory. Both heterozygotes and homozygotes can be detected.

Differences in biotransformation of isoniazid (INH) are caused by genetic differences in acetylation between individuals [24]. "Slow inactivators" of the drug ha e high blood levels, lack an acetylating enzyme in their livers and are homozygotes. Individuals who are heterozygotes have intermediate blood levels of the drug while homozygotes for the acetylating enzyme have low blood levels. Other drugs, such as some sulfa drugs, Hydralazine and Nardil, ppear to be inactivated by a similar mechanism. The frequency of peripheral neuropathy induced by INH is very much higher among slow inactivators than among rapid inactivators. The distribution of the various genetic classes is trimodal rather than unimodal when

appropriate tests are being used. There is a higher frequency of individuals with the acetylating enzyme in oriental populations. These findings are of general significance. Whenever a difference in drug response is seen between genetically differing populations and a discontinuous response is obtained when a sufficiently large number of individuals is studied, genetic differences can be expected.

Liver alcohol dehydrogenase is mainly concerned with breakdown of ethyl alcohol. The finding of an atypical alcohol dehydrogenase with higher *in vitro* enzymatic affinity for alcohol in some human liver specimens is of some interest [25]. Carriers of this mutation should be more tolerant of alcohol than the rest of the population. Many Japanese individuals react with marked vasodilation to the administration of alcohol. The mechanism is unknown and raises the question whether vasoactive peptides are released in these individuals. Further studies are indicated.

Drug resistance may be genetically controlled. Increased pseudocholinesterase activity is a rare mutation and causes succinylcholine resistance just as defective pseudocholinesterase activity causes succinylcholine sensitivity [18]. Marked resistance to the action of anticoagulant drugs, such as warfarin and dicumarol, has been observed as a rare mutation in one family [26].

The examples of genetically determined drug reactions may serve as models for the interaction of genetically determined biochemical variability with exogenous agents of disease. The enzyme abnormality alone is harmless as is the conventional dose of the drug. However, when the usual dose of the drug is given to an individual with enzyme deficiency, a drug reaction or disease occurs. Neither the genetic abnormality nor the drug alone cause difficulties. The administration of the drug to the genetically susceptible individual, however, causes disease. By analogy, other diseases may be caused by such interaction of environmental agents and genetic variability. In the more common diseases, however, more than a single enzyme abnormality may be expected, so that the constitutional basis of such diseases must be sought in the cooperation of several genetic factors rather than in a single specific enzyme deficiency.

Biochemical screening for inborn errors of metabolism [27, 28]. The brain is highly sensitive to various metabolic disturbances in the growing infant. Many different inborn errors of metabolism are associated with mental retardation. These include phenylketonuria, galactosemia, maple syrup urine disease, histidinemia, goitrous cretinism, homocystinuria, Hurler's syndrome, methemoglobinemia due to diaphorase deficiency, hyperuricemia associated with choreathetosis and self-destructive behavior, and several other amino acidurias. Mental retardation is also more common in some other hereditary disorders such as myotonic dystrophy, pseudohypertrophic muscular dystrophy, and neurofibromatosis. Although these conditions are not classified as inborn errors of metabolism, the existence of mental retardation suggests a more generalized systemic involvement affecting the brain.

In some diseases such as homocystinuria and methemoglobinemia due to diaphorase deficiency, mental retardation is only seen in some patients with the disease. The reasons for the presence or absence of

TABLE 1. *Urinary screening tests in some inborn errors of metabolism associated with mental retardation.*

Urine Test	Phenylketonuria	Histidinemia	Homocystinuria	Galactosemia	Tyrosinemia	Maple Syrup Disease	Hurler's Syndrome
Ferric Chloride Test	+	+	−	−	−	−	−
Cyanide Nitroprusside Test	−	−	+	−	−	−	−
Benedict Test	−	−	−	+	±	−	−
Nitrosonaphthol Test	−	−	−	−	+	−	−
Dinitro Phenylhydrazine Test	+	+	−	−	+	+	−
Cetyl Trimethyl Ammonium Bromide Test	−	−	−	−	−	−	+

mental retardation are not clear yet, but may be related to the interaction of the metabolic error with other genes predisposing to mental deficiency [24]. Prophylactic treatment involving dietary management is highly promising in phenylketonuria and galactosemia and theoretically helpful in maple syrup urine disease and homocystinuria. Early diagnosis is therefore mandatory so that treatment can be started as soon after birth as is possible. Bacterial inhibition assays are available for phenylketonuria, galactosemia histidinemia and maple syrup urine disease. The principle of these tests consists in suppression of growth of certain bacterial strains in the presence of some of the abnormal metabolites present in the blood of affected patients. Simple urinary screening tests are available to detect a variety of these disorders [28]. These tests can be done in any clinical laboratory and do not require specialized equipment (Table 1). Amino acid screening can be done chromatographically or with amino acid analysers in certain laboratories. Before potentially harmful treatment is started, consultation with a specialized laboratory is always indicated.

Several years ago, we developed a simple screening test for G6PD deficiency based on reduction of the dye brilliant cresyl blue [30]. The test has been widely used for the detection of G6PD deficiency but, along with other screening tests for this condition, must be used with caution during hemolytic episodes caused by the African type of G6PD deficiency when the older red cell population is destroyed and only young red cells remain in the blood. A normal screening test result may then be obtained in the presence of G6PD deficiency. A dye test based on the same principle has been devised by Beutler for galactosemia and may prove helpful in mass screening. Beutler recently also has developed simple fluorescence screening tests for the detection of red cell enzyme abnormalities which depend on conversion of the reduced pyridine nucleotides DPNH or TPNH to DPN or TPN.

It would be unwise at this time to pass laws regarding screening of all newborn babies for a variety of biochemical genetic diseases. Extensive studies need to be performed on an investigational basis to rule out some of the difficulties which may be expected in this work.

Carrier detection Population studies for gene frequencies and the requirements of genetic counseling make it desirable to have tests available for the detection of heterozygotes. If the enzyme or protein abnormality in a given disorder is known specific assays can be devised In general the enzyme level of heterozygotes is 50 % that of normals (acatalasemia methemoglobinemia due to diaphorase deficiency galactosemia pseudocholinesterase deficiency pyruvate kinase deficiency histidinemia) [31] This finding by itself is good evidence that regulation of enzyme activity occurs at the genetic level rather than by feedback inhibition. Overlap of heterozygote values with the normal range is observed in most disorders where enzyme activity was measured When a structural difference of the enzyme can be demonstrated as an essential part of the analysis (i.e. electrophoretic differences or the differential inhibition exhibited by pseudocholinesterase variants) such overlap disappears. The explanation for overlap between normals and heterozygotes on enzyme activity assays presumably relates to the existence in the normal population of several genetically differing enzymes with variable enzyme activity in the normal range [32] There is excellent proof for the existence of such isoalleles in the case of red cell acid phosphatase and highly suggestive evidence from correlation studies in relatives for glucose-6-phosphate dehydrogenase and pseudocholinesterase Other more indirect evidence suggests that the phenomenon of isoalleles may be quite general. When a heterozygote inherits a high capacity normal allele from one parent and a mutant allele with negligible activity from the other parent the level of enzyme activity in the heterozygote may be similar to that of normal individuals with two doses of low capacity isoalleles.

Carrier detection of autosomal recessive traits is genetically of great interest, but practically of less importance than detection of heterozygotes for X linked traits. The clinically normal sibs of patients with autosomal recessive disease have a 2/3 chance of being carriers. The chance that their mates are carriers equals the population frequency of the heterozygous state (i.e. 2% for phenylketonuria) Recurrence risk of the disease from such a mating is very low ($2/3 \times 1/50 \times 1/4 = 1/300$ for phenylketonuria) Sisters of patients with X linked diseases have a 1/2 chance of being carriers. If they are carriers, 1/2 of their sons will be affected—a much higher risk. Carrier detection of clinically important X linked diseases such as hemophilia and pseudohypertrophic muscular dystrophy has made some progress in recent years Antihemophilic globulin levels and creatine phosphokinase levels (as evidence of some muscle disease in clinically normal heterozygotes for muscular dystrophy) can be assayed. Apart from the potential problems posed by isoalleles, the effect of random inactivation of the X chromosome (Lyon hypothesis) adds a further complication to X linked carrier detection [33] According to this concept, approximately 1/2 of the maternal and 1/2 of the paternal X chromosomes in a given female are genetically inactive Depending upon the time of inactivation during embryologic development and depending upon possible selective mechanisms acting on these cell populations in later life, the ratio of active maternal to paternal chro-

zosomes may not be 50/50 but may range from 1/99 to 99/1. Consequently if in a given case most of the normal genes are active and the mutant genes are inactive, test results of such a heterozygote will fall in the normal range. However careful assay of a large number of known normals and obligatory heterozygotes should help to solve some of these problems and allow probability statements whether a given person with a value in the zone of overlap belongs to the normal or heterozygote population. Centralized specialized laboratories will be required for this important work.

Summary

1. The history of human biochemical genetics is reviewed with special references to Garrod's and Pauling's contributions.

2. Recent knowledge on the correlation of gene structure and protein structure is reviewed.

3. The influence of various mutations on the hemoglobin molecule is discussed. Heterozygote structural mutations affecting the critical active site of the hemoglobin molecule may lead to hemolytic anemia, drug sensitivity, polycythemia and methemoglobinemia. Other mutants are usually harmless. Another class of hemoglobin mutants—the thalassemias—cause diminished hemoglobin chain production and may lead to severe anemia in the homozygote state.

4. Many different glucose-6-phosphate dehydrogenase mutations have been discovered. Some are rare mutants, others are common and, as the sickle trait, owe their frequency to a selective advantage vis-a-vis falciparum malaria. The African type of G6PD mutant is caused by a structural mutation which causes more rapid degradation of the enzyme during red cell ageing. The chemically most unstable mutants are associated with chronic hemolytic disease.

5. Mutations of controlling elements as contrasted to structural mutations have not yet been proven in man, but hereditary persistence of fetal hemoglobin and orotic aciduria can best be explained by control mutations.

6. Differences in drug response and drug reactions may be caused by genetically determined biochemical variability. G6PD deficiency may cause drug hemolytic anemia. Pseudocholinesterase alterations may cause sensitivity or resistance to succinylcholine and differences in the acetylation of some drugs are genetically controlled.

7. Biochemical screening is feasible for a variety of disorders and is strongly indicated since certain forms of mental retardation may be prevented by early treatment, e.g. phenylketonuria.

8. Carrier detection of many heterozygote traits is possible. Overlap in enzyme activity between heterozygotes and normals may be caused by the existence of isoalleles in the normal population. Screening of heterozygotes of X linked diseases (muscular dystrophy and hemophilia) is practically more important in family counseling than screening for heterozygotes of autosomal diseases.

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On The Changing Patterns of Pediatric Practice

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Pediatrics as an important section of medical practice had its inception during the latter half of the nineteenth century At this time the principal concern was with physical illness and more with acute illness than with chronic disorders. The reasons were obvious. Morbidity and mortality rates at all ages of infancy and childhood, and especially within the first few years of life were extraordinarily high It soon became evident that reduction in the high incidence of infections and of nutritional diseases by preventive means had much greater potential for improving the child health situation than did currently available therapeutic facilities. It is noteworthy that in the leading textbook of Pediatrics (Holt) at the turn of this century there is no consideration of behavioral disorders.

The significant reductions in morbidity and mortality rates among infants and small children in the first twenty years or so of this century were undoubtedly due to a variety of factors, not all of which can be classified as medical or credited to the medical profession. In the main, the beneficial features were preventive and not curative in nature In addition to prevention of diphtheria and smallpox by specific immunization, of rickets and scurvy by specific nutritional supplements, and of infantile diarrhea in artificially fed infants by simple sterilization of their milk feedings, there were the general improvements in community sanitation and living standards. It is thus not difficult in retrospect to understand why the 1930's ushered in an era of therapeutic nihilism and attention was increasingly directed to a search for specific causes of diseases and to an understanding of the pathologic physiology which characterized them This too was the time of the first concentrated efforts to add guidance in child rearing to pediatric practice

The introduction of sulfanilamide in the mid thirties as the forerunner of specific antimicrobial agents and the subsequent isolation of corticotropin and the corticosteroids as well as the development of a wide variety of other effective therapeutic agents has restored drug and biologic therapy to an important place in medical practice but this time on bases much more substantial than had been conceived possible by most observers.

With the great reduction in serious illnesses among infants and children, the time and efforts of pediatric personnel began to be directed more intently to chronic diseases physical handicapping

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and mental retardation. These disorders which had received little attention have now come to be one of the major components of pediatric practice.

During the span of a century or so the pattern of pediatric practice has changed materially and especially so in North America. It is of interest that the patterns of pediatric practice which have evolved in the United States and Canada have differed rather significantly from those of many of the European and Asian countries, and to some extent from those of the South American ones. In the former the general pediatrician has become in large measure a general practitioner for children with heavy emphasis on the medical care of infants and young children rather than of the older ones. Since such care in recent years has consisted mainly of supervision of minor illnesses and of guidance in child rearing, the pediatrician in some respects is becoming as much or more oriented to the mother as he is to the child himself. By contrast, in many of the European countries the pediatrician serves mainly as a consultant to the general practitioner in the management of the more serious and/or more complex pediatric problems. Hence, in these countries the pediatrician remains somewhat more disease-oriented. But in all countries there has emerged a great interest in the various subspecialties of pediatrics such as neurology endocrinology hematology and psychiatry and a large number of comparatively recently trained physicians have elected to limit their medical activities to one of the relatively large number of subspecialties. Such physicians are now principally located in medical centers affiliated with medical schools.

The issue at the moment is not whether the practices of pediatrics have changed or are changing They have and are The issue at the moment is not even so much the current direction of change, but rather how extensive these changes will be how rapidly they can be accomplished with currently available personnel, and in what ways and to what extent educational programs should be altered to prepare medical and paramedical personnel for these prospective roles.

Critical to such planning is the recognition that pediatric needs differ sharply among peoples in high and low socioeconomic classes. While it is common to make such distinctions between peoples in the so-called privileged and underprivileged countries, it is just as necessary to be aware that such distinctions exist in significant measure within practically all countries, perhaps all save the smaller northern and western European countries. The great trend to urbanization has transferred much of the poorer rural population and added them to the slum dwellers of our larger cities. Unfortunately in the United States the majority of recently trained pediatricians who have gone into private practice have settled in the suburban areas where they can develop a busy practice among families of good socioeconomic status. Such practice can currently be quickly established and is relatively lucrative. As a consequence, the bulk of the people with low financial income and of poor educational status who have the greatest needs for health services and for guidance in health practices are inadequately served.

Until comparatively recently the private practice of medicine including that

of pediatrics, has been on a distinctly solo or individualistic basis with the majority of physicians being in the category of general practitioners The pattern has changed markedly and will probably continue to change Combinations of two or more doctors whose practice is limited to the same specialty was the first major step away from solo practice Then came medical centers to which the private physician could refer his diagnostic and therapeutic problems Those have been mainly associated with and are an integral part of medical school hospitals. But there have been detached ones, of which the Mayo Clinic in rural Minnesota is the best known example The private clinic pattern of practice is now taking hold, and especially so in the western half of the United States. Such clinics tend to have physicians trained in most of the specialties of medicine and some even have their own hospitals In some payment is on a fee-for service basis and in some it is on an annual contract basis

Whether the private individual practitioner is destined for extinction is a matter of conjecture It would be unrealistic to think that the traditional pattern of medical practice will be erased precipitously Moreover it would be most unfortunate if the role of the old family doctor who at his best, was physician, family counsellor and community leader were to be eliminated Certainly it has become impossible to be all things medically for the family unit. In addition, the current instability of neighborhoods resulting from the frequent movement of families from community to community within a given city and between cities does not permit the development of a permanent clientele by very many physicians.

Nevertheless, it seems not only important but essential that we retain the personal relationship of patient (and family) with one physician who sees and understands the patient as a person within his own sphere—family and community Within limits this personal arrangement should be possible in group practice. But if it is to be the policy of permitting the individual to select his own general physician within the clinic group, and even to change from one to another must be firmly established from the outset.

From limited experience the deduction has gained support that the general practitioner as he has been known, has little or no place in a relatively large medical group which operates as a private clinic Apparently such physicians do not effectively or comfortably work in conjunction with those trained in the various specialties of medicine and, on the other hand are less apt to be selected by patients for their general care than are the pediatricians and internists. This experience and evaluation of it is in part responsible for the suggestion that the next step in medical practice should be the creation of a new type of general practitioner who has had specialized training in general pediatrics and in internal medicine and who then could serve as physician for all members of the family unit Like the family doctor of old he could manage the common illnesses, provide child guidance and family counseling and in addition select and support the specialist whenever specialized medical services were required.

An important question of the moment is to what extent can the medical services

of the physician be supplemented and complemented to make the most effective utilization of his skills and to provide the patient with services which are best rendered by persons with special training for them. Such persons are currently designated as paramedical personnel, ancillary medical personnel or medical assistants. The designation is important only as it conveys to those who give and to those who receive the services an adequate concept of and respect for the various roles. Such personnel currently include the office nurse, the home nurse (Public Health nurse), the social worker the psychologist, the health educator the occupational therapist the physical therapist, the audiologist, the speech pathologist and therapist, and the nutritionist. To what extent some of these roles can be combined in individuals who work within private medical groups and what new roles will be created is a matter of conjecture at the moment and will be determined by experience and leadership. There is little doubt in the minds of many of us, however that the potential for improvement of medical services lies as much in the effective use of such ancillary personnel as it does in increasing the number of practicing physicians—perhaps more so. In this respect the private practitioner can borrow from the experience of the well organized hospital clinic.

One natural outcome of such a concept of medical practice is the development of the team concept of medical practice, especially for the management of chronic and permanently disabling conditions and for the solution and management of the more complex medical problems. Because in some instances such practice has resulted in fragmentation of service for the patient and his family and is often not only incomplete but not adequately explained to and understood by them the term "team has come under criticism, in some of our better medical units in which team work is highly effective for the more involved situations and in which patients have a distinct sense that their problems are thoroughly studied and managed, it is studiously avoided. In a sense this is unfortunate, since exactly what is needed is team work in the most complete sense conceivable. The solution appears to be relatively simple the personnel who participate in a given patient's medical care must work as a team in the strictest sense. But the team must in every instance have a captain. This leader should be the physician. Unfortunately all too many physicians are not adequate for such a role. They lack the qualities of leadership necessary for the personnel group and they do not appreciate the essentialness of providing an understanding explanation to the patient and his family do not know how to provide it or will not take the time to do it.

Training for such comprehensive care is essential and should begin in the undergraduate phase of the physician's education and in that of all members of the allied professional groups. Obviously such training should continue in the immediate postgraduate phases and thereafter through on-the-job experience and, periodically through postgraduate short-term courses or institutes.

For general pediatric care a specially trained medical assistant might prove to be the most useful person to be added in the next phase of development of medical

of pediatrics, has been on a distinctly solo or individualistic basis with the majority of physicians being in the category of general practitioners The pattern has changed markedly and will probably continue to change Combinations of two or more doctors whose practice is limited to the same specialty was the first major step away from solo practice Then came medical centers to which the private physician could refer his diagnostic and therapeutic problems These have been mainly associated with and are an integral part of medical school hospitals. But there have been detached ones of which the Mayo Clinic in rural Minnesota is the best known example The private clinic pattern of practice is now taking hold, and especially so in the western half of the United States. Such clinics tend to have physicians trained in most of the specialties of medicine and some even have their own hospitals. In some payment is on a fee-for service basis and in some it is on an annual contract basis.

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well it may be. The principal issue is whether the individual should retain some portion of responsibility for the cost of his own medical care. Except in the case of the medically indigent family it is my thought that he should. This stand does not exclude government participation but it is against the complete transfer of individual responsibility and the development of the philosophy of the welfare state. The situation at the moment is not a simple one. The medical profession as a group in the United States has not followed a course which has met fully the needs of all people. Perhaps it would have been better had the medical associations worked more closely with governmental agencies. In an ideal society, presumably a goal of civilized peoples, medical care of the best type would be available to those unable to pay for it as well as to those who can. In spite of some claims to the contrary there are many deficits. Where the present programs within the United States will lead is, of course, a matter of conjecture. In the current situation the government is trying to do more than is possible with available manpower and is not taking time for careful long range planning. Responsible medical leaders of other countries should pay close attention to and profit from our mistakes and failures as well as successes. It is unfortunate when, as in our case, there is so much political motivation behind presumed social progress. Legislation in respect to health matters is patently most difficult to control and will require the emergence of concerted medical leadership of a high order if recent mistakes are not repeated and confounded by those with short-range, selfish interests for their own personal power or for the over-development of their own institutions.

Pediatrics can and should play an important role in the current social evolution. If the preventable ills of infancy and childhood are to be controlled—and they will be—and if the birth rates within all countries are to be reduced to appropriate limits—and they must be—and if man's personal ambitions could be satisfied without infringing on the opportunities of other men of whatever country—and they must be if civilized man's goals are ever to be attained—then the role of pediatrics may become a much more limited one.

At the moment, however, the challenge to pediatrics encompasses all aspects of child welfare except that of formal education, and, even here, there is need for collaborative efforts. The relationship of physical fitness to learning potential is obvious, and perhaps of equal importance is the opportunity for the pediatrician to provide counsel in the formulation of the school's curriculum in health education and to attune his personal instruction of the children in his practice with it.

It is to the broad aspects of child welfare that pediatrics must give increasing attention. No longer can the pediatrician assume that he alone is sufficient to provide the health services now potentially available. Nor is this possible solely by the combined efforts of child psychiatrists and other physicians representing the many subspecialties of pediatrics, such as the neurologist and the endocrinologist. Rather, to be as effective as seems possible the pediatrician must recognize that pediatrics *represents* but one segment of the several professional groups which are now concerned with and operative in child

care. Such a person should be able to serve effectively as a visiting nurse within the home for carrying out special procedures and for instructing the mother in preparation of the milk formula in feeding and in such techniques as the taking of temperature and the giving of an enema and also as a psychologist and social service worker in assisting in the instruction of the parents in the philosophies and practices of child rearing and in an appreciation of the wide range of normal physical mental and social development Such a person would in the strictest sense have to be an essential member of a team with the physician. one in which each would know in detail what the other was doing The training for such an assistant to the pediatrician would have to be specially devised. It would include enough of nursing care to provide competence in the more simple techniques and an understanding of the child s and family s reactions to illness, irrespective of its severity special training to provide an adequate concept of growth and development so that she could be interpretive and adaptive for the parents of the guidance given initially and repetitively by the pediatrician and education to provide a philosophy of social responsibility which is centered individually in the family as the basic unit and socially within the immediate community as the larger unit

It should seem quite evident that if pediatric care can be truly contributive in child rearing the qualitative and quantitative needs of children in the under privileged classes should be much greater than those of families more privileged in respect to educational and economic status. There are of course sharp contradictions. Nevertheless the generality holds and ways must be found to provide the best of general and specific medical care and guidance for children of all classes Within communities of the lower socioeconomic classes there are probably more opportunities for medical assistants of all categories and especially specialized personnel such as public health nurses, social workers, health educators, psychologists and the like but it also seems reasonable that the specially trained general pediatric assistant as just described, could also be a useful adjunct In such a situation she might well be an intermediary between the physician and the more specially trained ancillary medical personnel on the one hand and the patient and his family on the other

The economic aspects of such medical care are also a matter of concern. It is not possible here to consider the many ramifications and the arguments for and against individual responsibility in contrast to financial support by the state for medical care The author may express his opinion, however that adequate utilization of medical services which are wholly state-supported requires a degree of social development and sophistication among people who are financially independent which is far from being universally achieved. Man seems to grow and develop as he assumes and successfully accomplishes tasks involving increasing responsibilities. It may be that one of the essentials for good medical care is the desire of the individual for it There is no doubt that so-called third party financial participation in medical care be it by private or public agencies is now integrated into the economic structure of most countries. And

all it may be. The principal issue is whether the individual should retain some portion of responsibility for the cost of his own medical care. Except in the case of the medically indigent family it is my thought that he should. This stand does not exclude government participation but it is against the complete transfer of individual responsibility and the development of the philosophy of the welfare state. The situation at the moment is not a simple one. The medical profession as a group in the United States has not followed a course which has met fully the needs of all people. Perhaps it would have been better had the medical associations worked more closely with governmental agencies. In an ideal society presumably a goal of civilized peoples, medical care of the best type would be available to those unable to pay for it as well as to those who can. In spite of some claims to the contrary there are many deficits. Where the present programs within the United States will lead is, of course, a matter of conjecture. In the current situation the government is trying to do more than is possible with available manpower and is not taking time for careful long range planning. Responsible medical leaders of other countries should pay close attention to and profit from our mistakes and failures as well as successes. It is unfortunate when, as in our case there is so much political motivation behind presumed social progress. Legislation in respect to health matters is patently most difficult to control and will require the emergence of concerted medical leadership of a high order if recent mistakes are not repeated and confounded by those with short-range, selfish interests for their own personal power or for the over-development of their own institutions.

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welfare The challenge would appear to be whether these various groups—pediatrics, public health nursing social service health education psychology and other ancillary medical personnel—can coordinate their efforts in effective ways which will make their joint services available to the private pediatric patient as well as to the one who is currently dependent upon public health facilities The responsibility of leadership in such collaborative efforts would appear to be most logically placed in the hands of the pediatrician. The extent to which pediatrics accepts this responsibility throughout the world and the objectivity with which such cooperative efforts are directed and carried out may well be a determining factor in the improvement of child health in all countries

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The Child with Down's Syndrome (Mongolism) His Parents, and the Community

by JAKOB ØSTER

Mongoloid children are from the very beginning quite special among the mentally retarded, they raise an immediate social problem, because the diagnosis can practically always be made at or shortly after birth. The characteristic appearance, possibly in association with chromosomal investigations, can establish the diagnosis with certainty to the experienced investigator. Even minor uncertainty should make the doctor refer the child to the expert, as diagnosis of Down's syndrome implies far-reaching consequences for both the child and the parents.

The first question to be considered is whether the parents should be informed. In my opinion the parents must be fully informed, as soon as the doctor is absolutely sure of the diagnosis, but it must be admitted that the communication is facilitated in the fortunately many cases, in which the parents themselves have suspicions that there is something peculiar about the behaviour of the child. From my own experience and investigations it is evident that the way of informing is at least just as important as the information itself. Extremes in the ways of informing the parents may be illustrated by the following examples: One doctor may say "A mongoloid of the worst type, prospects hopeless, send him away and forget him" another may say "Go home, love the child, and take care that you get other children". But none of these two methods is satisfactory. What many parents seem to miss is a sober statement of the condition, the possible cause; how a mongoloid child is; how the child may be expected to develop; whether the risk of having another mongoloid child is increased or not—and, after that, assistance and support, so that the parents may reach a well-considered decision on the solution of their problems.

The general improvement in the state of health and the decrease in mortality achieved in the last decades have been beneficial to the mongoloid children too. Certainly there are still many dying within the first years of life on account of congenital heart disease or infections to which many mongoloid children are predisposed. However, a recent English investigation has shown that four times as many mongoloids survived the first 10 years of life in 1959 as compared to 1929. There was a time when many parents were consoled by supposing that their mongoloid child would die early; this is no longer absolu

tely true thanks to therapy with antibiotics, which means that to-day there are perhaps more mongoloids in the community than before and that they have justified claims on the community

Why are mongoloid children weak? Predisposition to infections is presumably due to slow development bad respiration and difficulties in sucking and swallowing Mortality has proved to be different in mongoloids living at home from that in mongoloids placed in institutions. It is greatest in institutions, depending upon the degree of overcrowding and the available staff taking care of the children. This is partly due to the bigger risk of massive and recurrent infections, but also to psychic factors, because the child in an institution meets with a quite different way of life Similar problems arise when mongoloid children stay in hospitals we know that they behave and react quite differently from what they do at home and that under this psychic stress a restraint of all their functions takes place which may pave the way for decreased resistance to infections.

How are mongoloid children? This question may of course be answered here only fragmentarily As a matter of fact during the first months of life there are often problems no different from those presented by many children They differ from the latter only in that development is retarded in most respects. However their appearance is most often not very strange and they rouse the usual warm feelings in their mothers. It is most often the father who is unable to stand the situation, because he anticipates the sorrows to a much higher degree than the mother his thoughts reach far into a doubtful future while the mother is occupied with the child and her love of it. He is hurt in his pride, or sees his dreams concerning the child—especially when it is a boy—destroyed I feel convinced that often he is the one who should be consoled and supported, if the child's life is to take a harmonious course and this is not quite understood by many doctors. One thinks that it is the unhappy mother who needs support but if one probes under the surface experience shows quite another thing

And how are mongoloid children later on? To start with intelligence the fact is that the majority is mentally moderately deficient (67 %) a certain number severely (20 %) and a certain number slightly deficient (13 %) The highest I Q. I have met with in a 17 year-old mongoloid was 68. But rather more important than this graduation which is based on I Q.s is the fact that the possibilities of mongoloids for development and training in practical fields are considerably greater than those suggested by their I Q.s—if only they are offered the optimal conditions for developing Therefore most often it is not justified to speak of mongoloids and idiocy in the same breath as has been usual and is still done by some persons who are unacquainted with the matter And it is rather absurd to plead generally on the transfer of the mongoloid child to institutions immediately after birth as some doctors do only because these children are unlucky in that the diagnosis can be made as early as that This only expresses a regrettable lack of psychological insight and human understanding and missing knowledge of the facts, since at birth we can say absolutely nothing of the possibilities of the individual for development,

e can only say that the person in question will never be able to shift for himself in community—*but this is true of numerous other people*, and one would never dream of handling them in the same way—even if one could foresee their failure to manage in community. Furthermore we can only seldom predict the reactions of the parents.

It is usual to say that mongoloid children *are affectionate, happy and sensitive* that they have a sense of music and rythm, that they are enterprising, active and meticulous. At any rate, they may develop in this way under favourable conditions. And the few investigations which show that mongoloids do not differ in character or temperament from other mentally deficient individuals with the same level of intelligence originate from observations of patients who have for several years been placed in large institutions, and these investigations may just as well be interpreted to mean that they have not had the optimal conditions to develop their abilities, emotions and character.

Do mongoloid children *hamper* their parents? Yes, if the parents cannot accept the child as it is; if they cannot reduce academical ambitions in favour of affection and love; if they are ashamed and feel that *fate has treated them unfairly*, or if they differ in their opinion about the child. Finally it must be remembered that a mongoloid child may be born into a family already strained in various ways, and to such a family mongoloid child—or even a normal child—may be the last straw that "breaks the camel's back".

Do they hamper their sisters and brothers? Yes, if the parents cannot explain the situation to the other children and provide them with a harmonious existence. However the fear that the mongoloid child as such destroys the lives of sisters and brothers is greatly exaggerated.

Yet I want to emphasize that something special is required in order to make everything glide—qualities, the possession of which cannot be known beforehand.

Which are the optimal conditions for development of mongoloid children? To *this I must answer* quietly and with complete conviction, during the first years of life the child must live at home and must be nursed and cared for like other children in order to get all the stimulation offered at home. We shall have to remember that a home with a mongoloid child often has better possibilities than many others, partly because the members of the family are practically always of normal intelligence and finally because socially and economically they probably belong to a better off group.

But towards school age the problem arises that the child has to get together with other children and has to learn and *even the best home can seldom cope with* these requirements. The primary aim is to make the child capable of helping himself in daily life and to teach him to associate with others in a natural way. Whether the child must now be placed in an institution or not depends on the family environment and on the availability of necessary arrangements in the community such as kindergartens, schools, occupational centres and workshops. Mongoloids can benefit from all these. Many may utilize the kindergarten, some the school, *many the occupational* centres and several the workshop.

Now that we know a great deal of the

optimal conditions for development in mongoloid children, the question is inevitable why are so many mongoloids still often against the intentions of the mental deficiency service sent to large institutions—some of them immediately after birth?

As to the choice—home versus institution—mongoloids differ much from other mentally retarded in that as mentioned before the diagnosis of Down's syndrome can be made early because there are widespread delusions on the possible development of the mongoloids and because there is a widespread superstition that they carry with them misfortunes of all kinds to the home the sisters and brothers The parents attitude has in some cases, to be decided during the very first days of the child's life—especially when the child is born in a clinic. During this period the father and the mother are of course most sensitive and vulnerable and boundlessly much will depend upon communication with a responsible doctor A few words may lead to complete acceptation of the child as it is—or to its complete rejection. I shall not say which mental conflicts rejection may lead to, but I will add that parents who are persuaded to have their child removed and to forget it, have of course a demand for—and will also get, I hope—any support they need from their doctor and other authorities. Sometimes I get the impression that this group of parents has the greatest difficulties; just as we can talk about forgotten children, we can also talk about forgotten parents, and maybe here is an unsolved problem for both the institutions and the parents associations throughout the world.

In spite of all that has been said, mongoloid children will in many cases, be a greater burden to a home than is a normal child. Both psychologic factors and material considerations may under unfavourable conditions rightly tend towards placing a mongoloid child in an institution. In some cases the problems are so closely bound up with and dependent upon the parents personalities that it is the best solution for them—and thus it may be the best for the child too. By the way I believe that there exists an optimal time for placing in an institution those children, who must for some reason or another we cannot predict it with our present knowledge, but it is, at any rate, not in infancy

It is true that mongoloid children develop slowly and that they remain babyish for a long time if only for that reason, there is a great need of nurseries and kindergartens to relieve the mother so that she may perhaps take up her work which keeps her fresh or be free during some of her working hours at home. Direct financial support may also facilitate a difficult situation, and home counselling with advice for play occupation, toilet training eating habits, etc. may do the same All this is inexpensive help compared to costs in an institution, and I guess it will prove to be very effective in the future This is also the case with short stays in an institution in the event of illness in the child's home or in other special situations

All this aims at a trend to keep the mongoloid at home and to help him adapt to the community which is a way out from the former tendency to hide the child in a distant institution.

Certainly mongoloids can never grow

to be independent, but most of them can learn to manage in daily life and heavy scarcity of labour in countries like Holland has proved that mongoloids, too, can meet some of the demands of the assembly belt of existence—and of the Philips-factories, here among other things they are active collaborators in the production of television sets. This gives some idea of the simplicity of the single working process, of course, but it also shows that where there is real need, mongoloids can work on a par with normally gifted individuals. If we want to utilize their capacity for work, however we must take the consequences, offering them the optimal conditions for developing their abilities, as I have outlined them, and not leading them to a side-track from the very beginning.

I have mentioned shortly how and here mongoloids *can* be—not how and where they *must* be and I have mentioned what they *can*—not what they *must* do. I have tried to avoid generalization; but whenever we are confronted with a mongoloid child, we are forced to make a decision which will be of far reaching importance to the individual, his family and the community. In order to be of any help to the parents, the doctor must know much about mongoloids in general and about the individual patient in particular next, he must have an intimate knowledge of the practical support that may be obtained from the community through *external day arrangements o institutions.* And lastly but not leastly he must show in his medical care that the mongoloid child is just as valuable a member of the community and the human race as anybody else.

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As to the choice—home versus institution—mongoloids differ much from other mentally retarded in that as mentioned before the diagnosis of Down s syndrome can be made early because there are widespread delusions on the possible development of the mongoloids; and because there is a widespread superstition that they carry with them misfortunes of all kinds to the home the sisters and brothers. The parents attitude has, in some cases, to be decided during the very first days of the child s life—especially when the child is born in a clinic During this period the father and the mother are of course most sensitive and vulnerable and boundlessly much will depend upon communication with a responsible doctor A few words may lead to complete acceptation of the child as it is—or to its complete rejection I shall not say which mental conflicts rejection may lead to but I will add that parents who are persuaded to have their child removed and to forget it have of course a demand for—and will also get I hope—any support they need from their doctor and other authorities. Sometimes I get the impression that this group of parents has the greatest difficulties just as we can talk about forgotten children, we can also talk about forgotten parents, and maybe here is an unsolved problem for both the institutions and the parents associations throughout the world.

In spite of all that has been said mongoloid children will, in many cases, be a greater burden to a home than is a normal child. Both psychologic factors and material considerations may under unfavourable conditions rightly tend towards placing a mongoloid child in an institution. In some cases the problems are so closely bound up with and dependent upon the parents personalities, that it *is* the best solution for them—and thus it may be the best for the child too By the way I believe that there exists an optimal time for placing in an institution those children, who must for some reason or another we cannot predict it with our present knowledge, but it is, at any rate not in infancy

It is true that mongoloid children develop slowly and that they remain babyish for a long time if only for that reason, there is a great need of nurseries and kindergartens to relieve the mother so that she may perhaps take up her work which keeps her fresh or be free during some of her working hours at home Direct financial support may also facilitate a difficult situation and home counselling with advice for play occupation, toilet training eating habits, etc. may do the same All this is inexpensive help compared to costs in an institution, and I guess it will prove to be very effective in the future This is also the case with short stays in an institution in the event of illness in the child s home or in other special situations.

All this aims at a trend to keep the mongoloid at home and to help him adapt to the community which is a way out from the former tendency to hide the child in a distant institution.

Certainly mongoloids can never grow

TABLE 1 *Antitoxin titration by the serum neutralization test in guinea pigs Type of protocol used in the present study*

Test dose 1/10 unit toxin

Sera	Dilutions of sera under investigation							Results (units)
	0	1/5	1/10	1/50	1/100	1/200	1/400	
O Mother	–	–	+	+ +	+ + + +			1/20
O Newborn		–	+	+	+ + + +			1/20
R Mother		+ + + +	+ + + +	+ + + +	+ + + +			< 1/100
R Newborn	+	+ + +	+ + + +	+ + + +	+ + + +			< 1/100
Reference Antitoxin[a]			–		±	+	+ + + +	1/100

[a] Referred to the content of antitoxin units of each dilution.

ere read after 2-3 days. A typical protocol of such determination is shown in Table 1

Schick testing was performed in all mothers and their newborns, using diphtheria toxin of the Sela manufacturing company containing 1/30th of a unit per 0.1 ml. To eliminate possible pseudo-reactions a parallel control injection of heated toxin was always done.

Results and Discussion

Of the 161 mothers only 5, or 3.1%, had a definitely positive Schick test, whereas in another 9 the area of redness was less than 10 × 10 mm, but obviously more pronounced than that of the control injection. This obviously represents an extremely high figure for Schick negative adults since none of these mothers had been actively immunized.

When Zingher made his survey in New York in the early 20s (13) he found that 80 of adults were Schick negative. In 1948 Vahlquist (10, 11) stated that such a figure would not be found anywhere in the Western hemisphere. In an investigation he made in Sweden he found only 0 of adults with a titer of less than 0.02 units of diphtheria antitoxin per ml of serum (9)

In our patients the assay for diphtheria antitoxin showed a good correlation between mother and newborn. When mothers had a measurable antibody titer this was closely reflected in the fetal blood (Table 3)

Von Gröer & Kassowitz (5, 6, 7), studying the antitoxin level in 143 mothers and their newborns, found a closely related titer in 96% of their cases.

The Schick test in all newborns of our 14 positive mothers was unequivocally and uniformly negative (Table 2). This test which, as expected, was positive in mothers with an antibody titer lower than 0.01 units, was shown to be negative in respective newborns (Table 3). This is a difficult point to explain. Why should newborns with low diphtheria antibody titers behave differently on Schick testing than their mothers?

A review of the literature available to us revealed some conflicting data. It is generally accepted that a diphtheria antitoxin concentration of over 1/100 to 1/20 units per ml of blood ensures a negative

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Diphtheria Antitoxin Levels and the Schick Reaction in Mothers and their Newborns

by C. PAPADATOS G PAPAEVANGELOU and A KOUKOU

It is well established that infants at birth have circulating antibodies of maternal origin. These antibodies gradually disappear during the first few months of life, and are not usually measurable after 6 months of age As far as we know they represent passive immunity only and their presence in high concentrations during the first few months of life has been shown to be capable of interfering with active immunization.

The antibody pattern in the blood of the newborn depends upon such factors as type of maternal antibody placental permeability degree of fetal maturity and maternal antibody titer Diphtheria antitoxin belongs to a group of antibodies which easily cross the placenta When, therefore mothers have a measurable antibody titer this is obviously closely reflected in the fetal blood.

This paper was designed to study quantitatively the antibody status of the newborn as compared to maternal titers for a single antigen-antibody system namely diphtheria, and to evaluate the Schick test threshhold in mother and newborn in relation to the antibody titer

Materials and Methods

One hundred and sixty one mothers 16–47 years of age and their newborns were Schick tested on the 1st–5th day postpartum. These mothers were of a low socio-economic status and none of them had been actively immunized against diphtheria.

In 18 random cases diphtheria antitoxin was assayed in maternal and cord blood. Serum specimens were obtained aseptically from mothers and their newborns. They were kept at −20°C It is well known that no drop in the titer occurs when serum is kept at −20 for as long as thirty days.

As reference antitoxin we used the standard diphtheria antitoxin, containing 6 units per ml, whereas for diphtheria toxin we used the same toxin employed for the Schick test containing 1/50th of a unit per 0.1 ml.

Antitoxin was titrated by the serum neutralization technique described by Fraser [4] but guinea-pigs instead of rabbits were used By this method varying dilutions of serum were mixed with a known amount of toxin and injected into the skin of the test animal Four determinations were completed on each guinea pig and a parallel titration of the reference antitoxin was always done in the same animal.

As we were mainly interested in the area ranging from 1/30–1/100 units of antitoxin, the following dilutions of sera in saline were done 0 1/5 1/10 1/50 and 1/100. Results

Summary

One hundred and sixty one mothers and their newborns were tested for their Schick state. In [illegible] cases diphtheria antitoxin levels were determined in maternal and cord blood.

A Schick positive reaction was found in 11% of mothers. All newborns were Schick negative.

A good correlation was noted between maternal and cord blood antitoxin levels, as well as between the Schick state and the antitoxin titer in the mother. The discrepancy between antitoxin titer and the Schick reaction in the newborn is discussed.

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TABLE 2 *The Schick test in positive mothers and their newborns*

Case	Mother	Newborn
1	++++	−
	++++	−
3	++++	−
4	++++	−
5	++++	−
6	++	−
7	++	−
8	++	−
9	++	−
10	++	−
11	++	−
1	++	−
13	++	−
14	++	−

TABLE 3 *Correlation between Schick test and antitoxin level in mothers and their newborns*

	Schick test		Units of Antitoxin/ml blood	
Case	Mother	Newborn	Mother	Newborn
1	−	−	>1/10	>1/10
	−	−	>1/10	>1/10
3	−	−	1/10	1/10
4	−	−	1/5	1/[illegible]
5	+	−	<1/100	<1/100
6	−	−	1/10	1/10
7	±	−	1/[illegible]0	1/[illegible]0
8	+	−	<1/100	<1/100
9	−	−	1/10	1/10
10	−	−	1/10	1/10
11	−	−	1	1
1	−	−	1	1
13	−	−	>1	>1
14	−	−	1/2.5	1/2.5
15	−	−	1/2.5	1/5
16	−	−	1/[illegible]	1/[illegible]
17	−	−	1/10	1/10
18	−	−	1/10	1/3

Schick reaction. This is well documented by our results among tested mothers. Some workers however have reported a Schick negative reaction in persons with less than 0 005 units per ml of blood, as well as Schick positive cases with more than 0 05 units per ml of blood [8]

Wright & Clark [12] have reported a close correlation in the Schick test of mothers and their offspring in 84–85% among 713 tested infants. A discrepancy however has been reported between the results of skin testing in infancy and the presence of antitoxin in the blood, since a proportion of Schick negative infants were found to have little if any circulating antitoxin [8] Schick positive infants with a high antitoxin titer have not been reported up to now in the literature

Our results show that in the newborn there is no correlation between the Schick test and the antitoxin blood level. There are undoubtedly other factors, independent of antitoxin blood titer which determine the skin reaction

Cooke and others have reported similar results with the scarlatinal toxin [1 2 3] They noted that Dick negative newborns become positive at the age of six weeks to three months without change in their blood antitoxin levels.

From our findings we can assume that the Schick negative reaction in the new born infant does not necessarily reflect immunity to diphtheria It is a unique response of the infant s skin toward substances acting against it [9] Since immunologic phenomena in the newborn are so different from those seen in the adult we can not exclude the possibility that this non reactivity against diphtheria toxin is immunologic in nature Moreover since this insensitivity is extended to scarlatinal toxin and maybe to other substances as well more information is necessary to evaluate its nature in the problems of immunity in infancy

Summary

One hundred and sixty one mothers and their newborns were tested for their Schick state. In 18 cases diphtheria antitoxin levels were determined in maternal and cord blood.

A Schick positive reaction was found in 3.1 % of mothers. All newborns were Schick negative.

A good correlation was noted between maternal and cord blood antitoxin levels, as well as between the Schick state and the antitoxin titer in the mother. The discrepancy between antitoxin titer and the Schick reaction in the newborn is discussed.

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L'hypercalciurie idiopathique avec nanisme et atteinte rénale chez l'enfant

par PIERRE ROYER

L'hypercalciurie idiopathique sans hypercalcémie a été décrite par Albright en 1953 [1]. Chez l'adulte les circonstances pathologiques à l'occasion desquelles elle a été incriminée sont presque toujours la lithiase urinaire, beaucoup plus rarement l'ostéomalacie et la tétanie.

En 1962, Royer *et coll.* [10, 11] ont isolé chez l'enfant un syndrome caractérisé par une hypercalciurie idiopathique, un nanisme harmonieux, une ostéoporose, un défaut du pouvoir de concentration des urines et parfois une protéinurie de type tubulaire. Simultanément Gentil *et coll.* [5] ont décrit un syndrome identique mais où l'aspect radiologique du squelette était celui d'un rachitisme.

Des observations nouvelles, probablement analogues aux nôtres, ont été rapportées par A. Fanconi [4], Dent *et coll.* [3], Beilin *et coll.* [2], Nordio *et coll.* [9] et Jeune *et coll.* [6]. Ces observations ont démontré: 1° la variabilité du retard de croissance staturale; 2° la possibilité de l'ostéoporose et du rachitisme; 3° l'existence éventuelle de lithiase urinaire ou de néphrocalcinose; 4° l'apparition de ce syndrome quelquefois dès les premiers mois de la vie.

Parmi nos quatre observations primitives [10], l'une a été rejetée comme trop incertaine (obs. IV). Trois autres observations ont pu être analysées depuis. Nous avons vu apparaître dans un cas une néphrocalcinose qui n'existait pas initialement — (obs. II) et dans un cas un rachitisme vitamino-sensible hypocalcémique alors que l'aspect du squelette était primitivement ostéoporotique (obs. V). Dans le dernier cas, hospitalisé en 1966, une néphrocalcinose bilatérale intense s'est installée brusquement entre 9 mois et 18 mois d'âge.

L'étude des observations est résumée en trois parties: symptomatologie, physiologie pathologique, tentatives thérapeutiques.

Symptomatologie

Les circonstances de découverte sont le nanisme, ou une polyurie pitressoré-sistante ou un rachitisme ou des douleurs abdominales ou des crises de tétanie à répétitions dans les premiers mois de la vie.

L'âge où le diagnostic est porté va de 14 à 210 mois. Le sexe est 11 fois masculin et 2 fois féminin. Dans le cas de Beilin

Le père et un frère du malade ont une hypercalciurie. Chez un malade qui nous a été confié par Rossier et Job nous avons aussi trouvé une hypercalciurie chez le père et un frère.

1. *Nanisme*

Le nanisme est important dans presque toutes les observations. Il représente un *écart par rapport à la moyenne de l'âge* de 4 à 5 déviations-standard. Le poids est inférieur ou supérieur à celui correspondant à la taille. La maturation osseuse est toujours en retard par rapport à l'âge chronologique. L'âge osseux correspond souvent à la taille ou lui est un peu supérieur. La maturation dentaire est normale, en rapport avec l'âge chronologique. Le nanisme est harmonieux dans toutes les observations. Ces anomalies sont retrouvées par les autres auteurs, sauf A. Fanconi dont un des malades n'est pas nain.

2. *Anomalies squelettiques*

Outre le retard de l'âge osseux, l'examen radiologique du squelette montre le plus souvent une ostéoporose intense avec un abaissement du rapport cortico-diaphysaire au niveau des os longs et une diminution de la densité du squelette. Dans une observation, un rachitisme y est ajouté en cours d'évolution : il a guéri avec des doses physiologiques de vitamine D.

Toutefois d'autres auteurs ont noté un squelette normal [2] ou un rachitisme [3, 3]. Ce rachitisme est peu sensible ou résistant à la vitamine D.

3. *Anomalies rénales*

Dans tous les cas, il existe une *polyurie*, entre 000 et 500 ml par 24 heures. Dans nos cas, la densité urinaire maximale est entre 1010 et 1020 et la concentration osmolaire maximale est entre 170 et 778 mOsm/kg d'eau. Ce *défaut de concentration* est résistant à la pitressine. Il disparaît ou persiste, suivant les cas, lorsque la calciurie redevient normale.

La *protéinurie* existe dans deux cas sur cinq. Elle se situe entre 0,4 et 3 grammes par jour. Il s'agit d'une protéinurie de type tubulaire avec une globulinurie prédominante.

Les *fonctions rénales* sont satisfaisantes par ailleurs : urée et clearance de la créatinine endogène normales, absence de mélliturie et d'hyperamino-acidurie, pas de syndrome de perte de sel, kaliémie et kaliurie normales; épreuve au chlorure d'ammonium normale dans tous les cas.

Le *coefficient de réabsorption tubulaire* du phosphore est un peu bas et remonte de façon insuffisante lors de la perfusion veineuse de calcium.

Les *biopsies rénales* ont été faites dans cinq observations. Dans deux cas, elles sont normales. Dans trois cas, existe une néphrite interstitielle en foyers.

Les études cytobactériologiques des urines sont toujours normales. L'urographie montre des images non pathologiques. Dans une observation, une néphrocalcinose est apparue en cours d'évolution. Elle existait dès la première année de la vie chez notre dernier malade.

Les mêmes constatations sont faites par d'autres auteurs. Une lithiase avec néphrocalcinose existe dans l'observation 2 de A. Fanconi [4]; une néphrocalcinose nette est retrouvée dans le cas de Bellin [ ] et celui de Jenne [0].

4. *Hypercalciurie*

On peut parler d'hypercalciurie pathologique lorsque la calciurie dépasse 6

mg/kg/24 heures. La *calciurie* moyenne dans nos observations est entre 5 8 et 20 mg/kg/24 heures et la calciurie maximale entre 11 et 38 mg/kg/24 heures. L'hypercalciurie est stable ou variable suivant un rythme saisonnier élevée au printemps et en été plus modérée en période d hiver

La calcémie la phosphatémie les phosphatases alcalines du sérum la citratémie sont normales. Toutefois, dans une observation, la calcémie s est abaissée et une tétanie est survenue. Dans notre dernière observation la première manifestation a été une tétanie à l âge de 3 mois avec hypocalcémie.

Trois faits sont importants 1) la calciurie n augmente pas de façon sensible par des doses quotidiennes de vitamine D voisines de 10 000 unités par jour 2) la calciurie ne s abaisse pas sous l effet de l administration de bicarbonate de sodium contrairement à ce qui se passe dans l acidose tubulaire chronique idiopathique 3) la calciurie diminue par le régime pauvre en calcium le phytate de sodium l hydrochlorothiazide et le régime pauvre en chlorure de sodium

L interprétation de l hypercalciurie prête à deux ordres de discussion. D'une part nous ne l avons retrouvée dans aucune autre variété de nanisme endocrinien, viscéral ostéochondrodystrophique ou essentiel de l enfant D autre part la calciurie exprimée en débit par 24 heures peut etre augmentée dans les diabètes insipides sensibles ou résistants à la pitressine mais jamais au même degré que dans l'hypercalciurie idiopathique En outre la concentration du calcium exprimée par kg de poids et par litre d urine y est diminuée et non augmentée comme dans nos observations

Il convient de compléter cette symptomatologie en précisant que des examens nombreux ont permis d *exclure* 1) tout autre cause de nanisme 2) un syndrome de De Toni–Debré–Fanconi une acidose tubulaire un diabète insipide néphrogénique ou une cystinose 3) une hyperparathyroïdie 4) une sarcoïdose 5) une intoxication par la vitamine D

Physiologie pathologique

La physiologie pathologique de ce syndrome n est pas claire. Il nous paraît probable que l'hypercalciurie est le phénomène central expliquant 1 le trouble de concentration des urines, la protéinurie tubulaire la lithiase et la néphrocalcinose et les lésions éventuelles de néphrite interstitielle en foyer 2° le bilan calcique insuffisamment positif avec en conséquence le nanisme le retard de maturation osseuse et l ostéoporose Toutefois, tout ceci est encore hypothétique

Quant à l *hypercalciurie* elle peut etre liée à un état particulier du calcium plasmatique à une hyperabsorption intestinale à une affection primitive du squelette ou à un processus rénal primitif Les techniques utilisées pour étudier ces faits ont été exposées par ailleurs [12]

1 *État particulier du calcium plasmatique*

Ce fait a été insuffisamment étudié jusqu à présent La citratémie a toujours été normale Le calcium ultrafiltrable a été trouvé normal par Bellin [2] Le calcium ionisé dosé par la méthode de Soulié et Crosnier a été trouvé élevé dans deux de nos observations [12] Des études complémentaires sont nécessaires à ce propos.

— *Affection squelettique primitive*

Une ostéoporose idiopathique pourrait a priori être la cause d'une telle hypercalciurie. Bien que cette épreuve soit discutable, nous avons étudié le « pourcentage de calcium non éliminé dans les urines » au cours de la perfusion calcique. Ce pourcentage de calcium fixé » est entre 65 et 95 pour cent, c'est-à-dire correspond à celui des enfants normaux. Il n'y a pas là d'argument en faveur d'une ostéoporose primitive mais on ne peut pas l'éliminer. La réduction de l'hypercalciurie par le régime pauvre en calcium n'est pas en faveur d'une origine osseuse primitive.

Enfin, l'étude par les radioisotopes, effectuée dans deux de nos observations n'a pas montré d'anomalie de l'accrétion ni de l'ostéolyse.

3. *Hyperabsorption intestinale du calcium*

Des bilans de calcium et de phosphore ont été faits chez nos malades. Le bilan du calcium est entre — 98 et +128 mg/jour c'est-à-dire toujours insuffisamment positif ou négatif. Le pourcentage d'absorption digestive nette du calcium est normal dans trois cas 20, 22 et 23 pour cent et élevé dans deux cas 39 et 60 pour cent. Dans ces conditions, il est difficile d'admettre qu'une absorption intestinale excessive du calcium soit le phénomène primitif dans tous les cas. Les chiffres retrouvés par les autres auteurs sont toutefois sensiblement plus élevés 1, 35, 37 20 et 50 pour cent.

Enfin, la réduction de l'hypercalciurie par le phytate de sodium ou le régime très pauvre en calcium démontre l'influence de l'absorption intestinale sur la calciurie sans qu'il soit possible de conclure à ce certitude.

4. *Origine rénale primitive*

Nous n'avons aucun argument direct en faveur de celle-ci. Toutefois, il est possible que l'action de l'hydrochlorothiazide et celle du régime pauvre en chlorure de sodium s'expliquent ainsi. Nous allons l'envisager à propos de la thérapeutique.

Enfin, *deux constatations* méritent une mention. D'une part la citraturie le plus souvent normale est abaissée dans un de nos cas et dans l'observation de Nordio [9]. L'élimination urinaire des acides du cycle de Krebs, en dehors de l'acide citrique est normale. D'autre part, dans deux de nos observations, les urines ont une forte odeur aromatique. La réaction de Brandt est positive mais les chromatographies sur papier n'ont pas permis d'y retrouver de cystine ou d'acide cystéique en quantité anormale. La chromatographie des dérivés indoliques est normale.

Essais thérapeutiques

Divers essais thérapeutiques ont été faits. En principe, il convient d'abaisser la calciurie pour prévenir la lithiase et la néphrocalcinose et d'améliorer le bilan calcique pour permettre une croissance staturale et osseuse normale et éviter les anomalies de la structure du squelette.

1. La vitamine D. Elle améliore le bilan calcique sans augmenter la calciurie, même à des doses aussi élevées que 10 000 unités par 24 heures. Toutefois, dans une de nos observations, nous avons vu apparaître la néphrocalcinose sur les clichés radiologiques au cours de ce traitement.

— *Le régime pauvre en calcium*, avec un apport quotidien inférieur à 100 mg, diminue la calciurie en général après 5 à

10 jours de ce régime Toutefois, dans ces conditions étudié dans nos trois premières observations le bilan du calcium devient négatif ou très faiblement positif. Ce fait a été retrouvé par A. Fanconi [4] et par Bollin *et coll* [2] Le phytate de sodium a semblé plus intéressant à ces derniers auteurs

3 *L hydrochlorothiazide* à la dose de 5 mg/kg/24 heures abaisse nettement la calciurie D après notre expérience cet effet peut être transitoire Toutefois A. Fanconi a obtenu un effet durable chez un de ces malades [4]

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no chromosomal abnormalities have been detected.

From the clinical aspect there are three major systems affected, the respiratory tract, the gastrointestinal tract including the pancreas and liver and the eccrine sweat glands. Each system appears to present with different degrees of involvement and with no correlation with the severity of affection. For example the level of sweat electrolytes does not correlate with the degree of pulmonary or pancreatic involvement, nor does the extent of the pulmonary involvement bear any relationship to the pancreas or liver involvement. In addition, the onset of the symptoms varies considerably. In approximately 15% of patients with C.F. the disease process begins in utero, resulting in meconium ileus. In some individuals the symptoms appear in late childhood or early adulthood, as is seen with persistent bronchitis or bronchiectasis with nasal polyposis and sinusitis. The early onset of intestinal and pancreatic insufficiency in patients with meconium ileus is generally accompanied by a later onset of pulmonary disease in most cases [20]. Patients with meconium ileus have the same degree of elevation of sweat electrolytes as those patients in whom the onset of symptoms occurs at a later age. In about 10% to 15% of cases there is no detectable pancreatic enzyme deficiency even as late as 10 years of age. The pancreatic lesion may remain stationary or progress with no reversibility. On the other hand, the secondary pulmonary changes may be reversed to a certain extent by therapeutic measures. The sweat gland function is abnormal from the beginning [21] and remains so throughout life in close to 99% of patients with this disease.

These clinical observations suggest that a search for defects relating to the abnormal electrolytes in sweat or other tissue may provide a factor common to this disease. If such is the case, then we might consider this X factor as being grossly abnormal in the affected child, slightly abnormal or borderline in the heterozygote and normal in healthy individuals. This X factor would be expected to correlate with the severity of disease. Another consideration which leads us away from the pancreas and respiratory tract is the realization that clinical manifestations of those affected organs are secondary effects or complications of the disease process as contrasted to the unknown primary defect.

Although the sweat electrolyte levels provide a satisfactory way for the detection of the homozygous state in cystic fibrosis, this measurement is disappointing as a means of detecting the heterozygote. Di Sant Agnese who was initially impressed with this possibility stated that a significant proportion of relatives (both children and adults) of index cases showed an elevation of sweat electrolytes similar to that found in patients with C.F. [8]. Our earliest report in which the bag test was used was in agreement with Di Sant Agnese [22]. However subsequent studies involving much larger groups of relatives of patients with C.F. and using other methods of sweat stimulation failed to confirm those initial observations [17, 23, 24, 25, 28]. A recent compilation of our sweat test in 73 parents using pilocarpine iontophoresis showed a mean chloride of 33.2 ± 15.5 mEq/l and sodium of 54.9 ± 19.6 mEq/l. An adult control group of 63

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From the Division of Clinical Laboratories and Research and Department of Medicine Children's Hospital Medical Center and Department of Pediatrics, Harvard Medical School and Children's Cancer Research Foundation

Some Genetic Considerations in Cystic Fibrosis A Study of Nail and Sweat Sodium in Two Sibships[1]

by HARRY SHWACHMAN and LOUIS KOPITO

Cystic fibrosis, transmitted as an autosomal recessive trait is one of the most common hereditary diseases in the United States and Western Europe The incidence of cystic fibrosis (C F) in Caucasians has been estimated as ranging from 1 in 400 to 1 in 3700 live births [1 2 3 4 5 6] Our estimate of the incidence of the disease in our community is approximately 1 in 1000 live births. Andersen of New York City [1] estimated an incidence of 1 in 600 in 1946 Accordingly one person in every 16 carries the gene for cystic fibrosis In spite of the relatively widespread prevalence of this gene attempts to detect the heterozygote have been unsuccessful Some authors have stated that parents of children with C F have a significantly elevated sweat sodium and chloride and also have a higher incidence of certain conditions, such as diabetes mellitus, emphysema chronic bronchitis or other forms of chronic pulmonary disease or conditions affecting the intestinal tract such as ulcers and biliary tract disorders [7 8, 9]. The suggestion has also been made that C F plays a significant role in the etiology of chronic bronchitis, peptic ulcer and diabetes mellitus in adults [10 11 12 13]. These reports were critically reviewed by di Sant Agnese & Powell in 1962 [14] leaving this question unresolved We have examined a number of parents of children with C F for the diseases or conditions which were stated to occur with higher frequency in this group Our experience confirmed by Batten *et al.* [15] fails to substantiate these claims We also included pulmonary function tests and sweat tests by the pilocarpine iontophoresis method [16] The findings in sweat are similar to those of other investigators [1 18] and showed no significant differences in the parents and control groups. A recent study [19] in which 132 parents and 118 controls were compared for various acquired diseases particularly of the respiratory and gastrointestinal tract, confirmed the above

At present we are not aware of any metabolic or enzyme defect in cystic fibrosis which would account for the clinical expression of the disease. Mo-

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Table 2. Sodium and potassium in finger and toenail clippings from children born to fathers or mothers with C F

Identification	Age	Sodium mEq/Kg	Potassium mEq/kg	Relationship
1. X 822, K. G	3 yrs.	60	24	Daughter of C.F mother
X 822, K. G.	4½ yrs.	43	26	
2. X 780, D K.	6 mos.	113	73	Son of C.F mother
3. X 781, M. R.	12 yrs.	119	84	Son of C.F mother
4. X 640, K. M.		174	170	Son of C.F mother
4. X 670, E. K.		218	84	Son of C.F mother
6. X 1014, J G.	16 yrs.	337	97	Daughter of C F father
7. X 821 J S	9 yrs.	103	83	Son of C.F mother
8. B 111, F F (hair specimen)	17 hrs.	119	4.3	Son of C.F Mother 7 mo. premature, died at 17 hrs.

83, and 98 mEq/l, and very minimal pulmonary symptoms. We cannot make the diagnosis of cystic fibrosis or exclude it with our current information in these three patients. The demonstration of elevated sodium values in nails of the healthy siblings suggested that this analysis may offer clue to the detection of the heterozygote. We accordingly analyzed the nail clippings from 8 known heterozygote infants born to seven mothers and one father with C.F Out of the 8, 7 healthy children showed no evidence of C.F and had elevated nail sodium levels ranging from 108 to 337 mEq/kg (Table 2) In investigating parents of children with C.F (known heterozygotes) we were unable to demonstrate elevated nail sodium concentrations beyond establishing a statistically significant difference in the mean values as compared to those obtained in an adult control group. The range of values obtained in both groups overlapped considerably making it virtually impossible to single out the individual heterozygote for the C.F gene. In searching for an explanation we are studying the effect of age on nail sodium levels. We observed only a small decrease in the level of nail sodium as function of aging

In order to learn more about the nature of the accumulation of sodium in nails and the factors which may produce changes such as diet and environment, we have been observing several families with C F children of different ethnic backgrounds, and residing in widely separated areas. All available immediate relatives of the index case including grandparents, uncles, aunts and first cousins, were given sweat tests and had their nail sodium quantitated periodically Two of those families are selected for illustrative purposes, as seen in Charts 1 and 2 The proband is identified by an arrow The three generation studies are marked I II, and III and denote. (I) grandparents, (II) parents uncles and aunts, and (III) patients, their siblings and cousins. The nail sodium concentration in mEq/kg appears in the left upper corner of the square for males and the circle for females. Sweat sodium levels in mEq/liter are shown in the lower left corner under the nail values. The age, in years at the time of observation, appears outside the square or circle in the upper

TABLE 1 *Distribution of sodium in fingernail and toenail clippings*

	Number	Sodium Mean mEq/Kg	Sodium Range mEq/Kg	Sodium Standard Deviation
1 Patients with C.F	42	232	81–610	104
2. Healthy children under 17 years	63	66	11–700	36
3. Parents of children with C.F	171	74	11–350	40
4. Healthy adults	51	71	11–150	30
Siblings of patients with C.F	184	103	10–320	58

persons had a mean chloride of 29 7 ± 17 7 mEq/l and sodium of 46 8 ± 21.5 mEq/l The small differences between the mean values are not statistically significant.

In view of the elevated sodium in the sweat of patients with cystic fibrosis and the normal or former controversial finding in heterozygotes, we and other investigators have studied sodium in a variety of body fluids and tissues to see if abnormal values would be found The materials studied included serum erythrocytes, urine saliva tears duodenal fluid meconium hair nails, skin and muscles. Except for the markedly elevated sodium in hair and nails, and the reduced value in meconium [20] we found no significant difference which could distinguish individuals with cystic fibrosis on the basis of the sodium concentration in these tissues

Finger and toe nail clippings appeared to store sodium in a manner which provided good differentiation of the patients with C.F [27] A more recent summary which included the total sodium in the nails and nail wash shows that out of 242 patients with C F 231 or about 95 % had nail sodium levels in excess of 110 mEq/Kg of nails. Only 11 patients had values between 80 and 110 mEq/Kg (Table 1) The mean values for the patients with C F was 232 mEq/Kg with a standard deviation of ± 104 In contrast, a group of 63 healthy children under 17 years had a mean nail sodium of 66 ± 30 mEq/Kg We also studied 51 healthy adults, 184 siblings, and 171 parents of the patients and found statistically significant differences between the mean nail sodium levels of all the groups.

On the basis of these observations made over the past three years, we concluded that this test may be a useful diagnostic aid in confirming the clinical impression of the disease It is of definite value in patients showing equivocal sweat sodium levels. When the nail sodium is less than 80 mEq/Kg we can exclude the disease with over 95 % certainty Of special interest are the findings in siblings. The sodium values extend over a large range from normal values seen in healthy subjects to elevated values observed in patients with C F All siblings whose nail clippings were analyzed were seen clinically and subjected to the pilocarpine iontophoresis sweat test. Of the 184 siblings, 181 were healthy and free of respiratory or pancreatic disorders and had normal sweat tests Three had elevated sweat sodium levels, namely 71

TABLE 2.—*Sodium and potassium in finger and toenail clippings from children born to fathers or mothers with C F*

Identification	Age	Sodium mEq/Kg	Potassium mEq/Kg	Relationship
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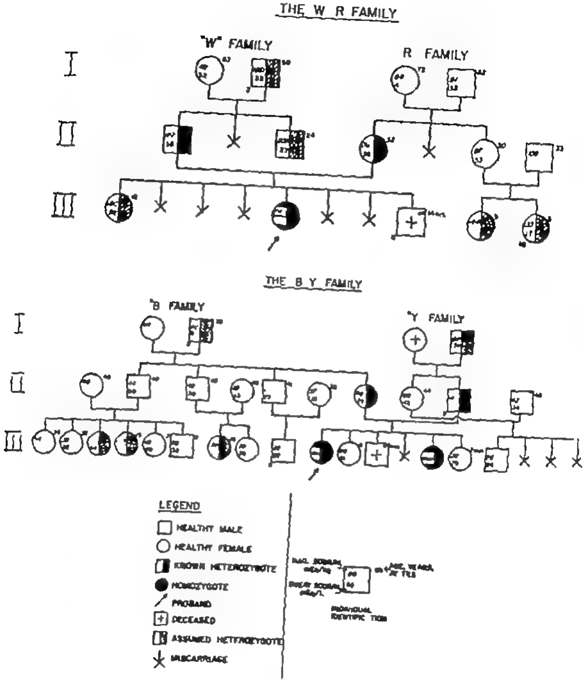

right The individual s identification number is shown in the lower left corner An illustrative example appears in the legend The known heterozygotes are the parents of the proband. At least one of the paternal as well as one of the maternal grand parents must be a heterozygote in order to transmit the *C F* gene to the parents of the affected child. *Half* of the children born to these grandparents, i e the parents of the patients and the related uncles and aunts are heterozygotes Accordingly the expected *statistical* frequency of the heterozygote sibling of the patient with

C.F is 2 1 i.e. for every child with C.F two siblings are expected to carry the gene, and one sibling is expected to be normal. The healthy siblings with normal sweat and elevated nail sodium values are assumed to be heterozygotes and are identified graphically as shown in the legend.

The observed values are presented in Charts 1 and 2. A study of the Chart of the W R families shows nail sodium values which demonstrate a theoretically "ideal pattern for the recognition of the heterozygote. The proband, III-5, was diagnosed as having C.F at age one year in 1957 at which time the sweat sodium was 109 mEq/l. The nail analysis done in 1965 showed a sodium concentration of 243 mEq/Kg. The family history revealed that out of 8 pregnancies 5 terminated in miscarriages, and the last infant died at 14 hours. This mother was Rh− and the father Rh+ and during her last pregnancy she developed a high antibody titre. An older sibling, III 1 was subjected to a sweat test when the proband was diagnosed in 1957 and the results showed a sweat sodium of 23 mEq/l. A second sweat test in April 1966 revealed a sodium value of 33 mEq/l, well within the normal range. The nail sodium at this time was markedly elevated, 180 mEq/Kg, and this child was accordingly considered to be an assumed heterozygote Both parents, II 1 and II-4 were sweat tested in 1957 and again in 1966 with normal values. The nail sodium determined in 1966 was markedly elevated and fits the criteria for selecting the heterozygote. In studying the grandparents of the proband we observed normal sweat and nail levels in I 1 and normal sweat with elevated nail sodium in I 2. The grandfather (I *) is, therefore designated as being an "assumed heterozygote The maternal grandparents I-3 and I-4 had normal sweat values but only slightly elevated nail sodium values. The level of these 84 and 91 mEq/kg, fall in the 'borderline zone of 80 to 100 mEq/Kg, between the C.F and normal populations. Values in this range are hard to interpret. Although we know that one of the maternal grandparents must be a heterozygote, the nail sodium levels were not sufficiently elevated to have one of them so designated.

Other observations of interest are those pertaining to the proband s cousins, III 9 and III 10 both of whom have normal sweat levels and slightly elevated nail sodium The values of 144 and 133 mEq/Kg are sufficiently elevated to justify their designation of assumed heterozygotes within the context of this study The proband's uncle II-3, had markedly elevated nail sodium but normal sweat sodium The proband s aunt, II 5 had normal sweat sodium and borderline nail sodium. In this family we observe a generally elevated nail sodium pattern common to all relatives of the proband with the exception of the paternal grandmother I 1

The pedigree of the B.Y family is shown in Chart 2. Only the proband s father II 9 had elevated nail sodium whereas the mother s values were within the range generally seen in a control population. Both children with C.F., III 10 and III 14 have nail sodium levels in the lower 10 % of those common to patients with C.F The grandfather I-4, has both elevated nail and sweat sodium values and gives a history of good health. The maternal grandfather has a nail sodium of 90 mEq/Kg which is in the border line range. Since at least one of the 'B

grandparents is a heterozygote the grand father with the relatively high nail sodium was so designated. Although none of the uncles and aunts had unusually high nail sodium levels three cousins III 3 III-4 and III 7 had elevated nail sodium with normal sweat sodium. If we consider the cousins as being heterozygotes on the basis of the elevated nail sodium their fathers *II 2* and *II 3* should also have had eleva ted nail sodium for they too must be heterozygotes in order to transmit the gene to their children. We are unable to explain these variations from the expec ted patterns of nail sodium in the mother of the patient II 7 and her brothers II 2 and *II-3*

We expect to follow the siblings of the patients with C F which we designated as assumed heterozygotes on the basis of their elevated nail sodium and normal sweat sodium through adulthood and marriage If our assumptions are correct half of their children will have elevated nail sodium and normal sweat values provided their partner does not carry the gene for C F Also as they age their nail sodium levels will diminish until they reach levels which will overlap into a control population range The decline in concen tration of nail sodium with increasing age does not explain the difference noted between parents and healthy adults, thus signifying that this type of assay does not detect the heterozygote in adults In the meantime should a satisfactory meth od be found to detect the heterozygote, its application to these well-studies and cooperative families may be undertaken.

Summary

The rationale for studying tissue that stores sodium as it occurs in nails is presented. The results of our studies on the concentration of sodium in 242 patients with C F., 63 healthy children, 171 parents of children with C F 51 healthy adults and 184 siblings of patients with cystic fibrosis are presented. The elevated nail sodium concentration was detected in over 95 % of the patients with C F and in no patient with C.F was the value less than 80 mEq/kg Seven out of 8 children born to parents, one of whom had C.F showed elevated nail sodium By defini tion these healthy children are the only presently recognized heterozygotes in in fancy The sibling group showed a wide range of values suggesting the possibility of indicating the heterozygote

The nail and sweat sodium results in three generations of two selected sibships is shown in graphic form. Variations are noted which indicate that this type of study does not select the heterozygote for the gene of cystic fibrosis.

The usefulness of the measurement of nail sodium is stated It is hoped that this report will stimulate others to seek other methods for detecting the heterozygote

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Familial Leukaemia — Three Cases of Acute Leukaemia in Four Siblings

by K. M. LUNDMARK, ASTRID THILÉN and B. VAHLQUIST

The significance of genetic as compared with environmental factors for the development of leukaemia in man will remain a matter of speculation until our basic concepts have extended considerably further than they have hitherto. By reporting the occurrence of an accumulation of leukaemia cases in the same or successive generations of a single family further perspective on the problem can be achieved. Such reports of familial leukaemia have been recently summarized by Gunz *et al* [7] and Iversen [10] and to their list we now add a family in which three of four siblings died from acute leukaemia.

Case Reports

Notes on the family. This is a family living in a medium-sized factory town in southern Sweden. There is no consanguinity and there have been no other cases of serious blood diseases known among the relatives of the family. The father works in a carton factory and the mother is a housewife. As far as is known, there were no congenital malformations nor exposure to leukaemogenic agents among any of the family members. The pedigree is shown in Figure 1.

The twin brothers, siblings 1 and 2, were regarded as binovular twins since fourfold fetal membranes and double placentas were found at delivery. However they had rather similar physical features and were of the same blood group (O Rh positive). It has not been possible to add further evidence of their zygosity after so many years and interviews with the parents about these problems have been avoided for psychological reasons.

Sibling 1 (born 9/4/47). Pregnancy and delivery were normal. His birth weight was 2.6 kg. He appeared healthy apart from a tendency to mild recurrent upper respiratory infections. In July 1951 considerable enlargement of lymph glands, especially the cervical ones, was noted and after a month when fever supervened, the boy was admitted to the local hospital. Physical examination revealed pallor and enlarged lymph glands, but the liver and spleen were not palpable and there were no signs of bleeding. The laboratory findings were: haemoglobin 9.5 g/100 ml, leucocytes 5,100/mm with 42% lymphocytes and 32 % undifferentiated blast cells, platelets 169 000/mm and sedimentation rate 56 mm/h. A bone marrow aspirate was richly cellular with undifferentiated blast cells as the dominating cell type. The boy was treated with penicillin for two weeks, the fever disappeared and he was sent home. After a further two weeks a pronounced anaemia (haemoglobin 4.5 g/100 ml) and a moderate hepatosplenomegaly were noted and he was given a blood transfusion. A therapeutic trial with urethane (1 g daily) had no noticeable effect and repeated transfusions had to be given. No tendency to

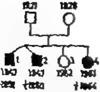

Fig. 1. Pedigree of the family. Year of birth is indicated for all members and year of death for those who died of acute leukaemia (solid symbols).

bleeding was seen. He died 3 months after the initial diagnosis. No autopsy was carried out.

Sibling 2 (born 9/4/47). Pregnancy and delivery were uncomplicated; birth weight was 2.5 kg. He was healthy until mid-January 1950, when he appeared pale and tired. When he was investigated by a physician two weeks later a moderate anaemia (haemoglobin 10.6 g/100 ml) was the only abnormal finding. However the child became febrile and more tired and after a further three weeks he was admitted to hospital. On examination he was pale with moderately enlarged lymph glands, spleen and liver and sparse purpura. The haematological data were haemoglobin 7.7 g/100 ml, leucocytes 18,100/mm³ with 80% undifferentiated blast cells, and sedimentation rate 53 mm/h (platelets not counted). A bone marrow smear was typical of acute leukaemia with marked dominance of undifferentiated blast cells.

The child was sent home after a week on urethane therapy (1 g daily), but no improvement was noted. After five weeks he was again admitted to hospital because of vomiting and pallor. The anaemia was pronounced (haemoglobin 2.0 g/100 ml) and blood transfusion was given. Two weeks later he had sustained high fever and he died at home two months after diagnosis. No autopsy was performed.

Sibling 3 (born 8/51). This girl is now 15 years of age and appears quite healthy.

Sibling 4 (born 10/16/61). Pregnancy and delivery were uneventful. The birth weight was 3.1 kg. She had some minor allergic symptoms, but was otherwise healthy until December 1963 when she became tired. In January 1964 her condition deteriorated with enlargement of the lymph glands and on admission to hospital, hepatosplenomegaly was also noted but no signs of bleeding. Initial blood findings were: haemoglobin 4.9 g/100 ml, leucocytes 148,000/mm with 95% undifferentiated blast cells, platelets 4,000/mm and sedimentation rate 57 mm/h. A bone marrow aspirate revealed a leukaemic picture with almost only undifferentiated blast cells.

The child was given blood transfusion and steroids (triamcinolone 20 mg daily) and improved rapidly with an almost complete remission. Maintenance therapy with steroids was tried, but after two months there was a relapse with a high number of leucocytes, mainly consisting of leukaemic blast cells. A moderate improvement occurred after increased steroid dosage, but one month later both blast cells and anaemia were noted in the peripheral blood. Repeated blood transfusions were given and four months after the initial diagnosis mercaptopurine (37.5 mg daily) was started. A pronounced pancytopenia developed and the mercaptopurine was discontinued.

Five months after diagnosis the patient was admitted to the Paediatric Clinic, Uppsala, for further study. She was extremely cushingoid and a moderate hepatosplenomegaly and minor bleeding signs were noted. There were very few leucocytes and platelets in the peripheral blood but normal haemoglobin (due to recent transfusions). A bone marrow aspirate, however, was hypercellular with numerous leukaemic blast cells, and mercaptopurine and prednisone were given again. Within a few days there was a rise in the numbers of platelets and granulocytes and after two weeks reticulocytosis, and she was sent home. Chromosome analyses of cultured leucocytes showed a normal female karyotype.

The patient underwent a partial remission lasting nearly two months. Thereafter a relapse occurred with pronounced pancytopenia except for high numbers of blast cells. Increased doses of [illegible]

TABLE 1 Clinical data of three siblings with acute leukaemia

Sibling (date of birth)	Sex	Age at diagnosis (years)	Duration of symptoms before diagnosis (weeks)	Type of leukaemia	Therapy	Survival after diagnosis (year)	Comments
1 (9/4/47)	M	3 11/1	4	Acute undifferentiated blast leukaemia	Urethane	3/1	Twins, probably binovular
2 (9/4/47)	M	5/1	3	Acute undifferentiated blast leukaemia	Urethane	*/1*	
4 (10/16/61)	F	3/1	4	Acute undifferentiated blast leukaemia	Corticosteroid mercaptopurine	8/12	Chromosomal study: normal female karyotype

purine had no effect and the patient died eight months after the initial diagnosis. Autopsy revealed marked leukaemic infiltration of the bone marrow and parenchymatous organs and generalized minor bleeding.

Some relevant data concerning the affected children are given in table 1. It appears that all three siblings had many clinical features in common including morphological type. The bone marrow smears from the twin brothers have been reexamined.

Discussion

The idea of a genetic factor as a subsidiary mechanism in the aetiology of leukaemia in man has its origin in observations of the following character.

1. *Epidemiological studies.* The first large study was reported by Videbaek [20]. He found an overrepresentation of leukaemia and malignancies among the relatives of the leukaemia patients (8.1 %) compared to controls (0.5 %). The conclusions drawn from these results have not been free from criticism [10], but the basic observation has been supported by studies of more recent years and thus seems to be valid [21, 13].

2. *Reports of accumulated cases in a single family.* The overall risk of contracting leukaemia is, fortunately, low. In a study on a well-defined Swedish population group the risk of contracting acute leukaemia below the age of 15 years was found to be 0.04 % [3]. The occurrence by mere chance of two cases of acute childhood leukaemia in a sibship should thus be extremely rare. With 3 or more cases specific factors must almost certainly have been operative in the causation of the leukaemia.

In a recent paper by Gunz *et al.* [7] describing 4 (possibly 5) cases of acute leukaemia in a Maori family with 8 children references are made to nine earlier papers on the subject of familial occurrence of the disease (three or more cases). Further observations are probably to be found in the pertinent literature and it is almost

certain that an undefined number of observations will have never been published.

3. *High concordance rates in leukaemia in monovular twins.* An interesting review on this subject has been made by MacMahon & Levy [14] in their analysis of a large series of cases from the United States. They found that when a monovular twin contracts acute leukaemia in childhood, the probability is as high as 25% that the co-twin will develop the disease. In their five sets of monovular twins, both affected, the time interval between the onset of the disease in the first and second twin was from 0 to 10 months (mean 7 months). In each set it was evident that both children had the same type of leukaemia.

However Barber and Speirs [1] and Court Brown & Doll [4] failed to find one single pair of twins, both affected, in their very extensive series from Great Britain.

4. *Higher incidence of acute leukaemia in children with Down's syndrome.* This finding is now well documented, and the risk among children with mongolism has been shown to be about 20 times greater than that of the general population [6].

Miller [16] has recently reviewed the excessive frequency of leukaemia in children with genetically induced diseases.

It is of some interest to determine whether under the circumstances mentioned in points 1–4, leukaemia exhibits any special characteristics.

In unselected series of childhood leukaemia reported by Oehme [18], Hug [9] and Iversen [10] altogether 830 cases, only about 5 % had developed the disease before the age of one year. Among the children with Down's syndrome combined with acute leukaemia, however, in several cases the leukaemia was either present at birth or had its onset during the first year of life [10]. Among the few families with several cases in the same sibship, one is reported [ ] in which 3 out of 5 siblings were shown to have the disease already during the first few months of life.

Familial leukaemia is usually of the same type in the individual cases of the reported families, being generally lymphocytic (lymphoblastic, nondifferentiated blast leukaemia) as also are most cases of childhood leukaemia. However, in congenital leukaemia and the leukaemias in children with Down's syndrome the proportion of the myelocytic type is far larger than in a collected childhood series [10].

In general no correlation has been found between acute leukaemia and congenital malformations other than Down's syndrome [1]. Miller [15] however noted twice as many major congenital defects among leukaemic children as among matched controls, and also an increased incidence of Down's syndrome among siblings of leukaemic children. He suggested that childhood leukaemia was part of a constellation of familial disease.

Chromosomal changes in acute leukaemia are frequently reported but show a great diversity and do not appear to be specific [11]. None of the familial cases with acute leukaemia so far examined have shown any chromosomal abnormality [5]. However, in a familial accumulation of chronic lymphocytic leukaemia an inherited chromosomal abnormality has been reported [8].

In the family described in this report there was no known consanguinity nor

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blood dyscrasias. The disease did not differ from ordinary acute lymphoblastic leukaemia with respect to time of onset clinical course or morphological type Two of the siblings were twins, but probably binovular as also were the affected twins in the family described by Gunz *et al.* [7] In our cases the interval between the onset of illness in the first and second twin was 18 months and in the report of Gunz *et al* 21 months

In the pertinent literature considerable interest is paid to the possible influence of noxious factors in the environment [16 17] Such factors may also explain the familial occurrence of a certain disease as an alternative to genetic mechanisms [12] However toxic factors are much more prone to cause aplastic reactions rather than leukaemia In the familial cases irradiation has never been seriously incriminated. We have no reason to suspect any exposure of the members of the reported family to such toxic or irradiating factors.

There is reason to hope that it will not be too long before the aetiology of acute leukaemia in human beings will be seen in a more clear light Even if the hypothesis of viral aetiology gains further support, it will nevertheless be difficult to explain clinical observations of the nature discussed above without the assumption that at least in certain cases, genetic factors must be of some influence.

Summary

An instance of familial leukaemia is described where 3 children out of 4 died of acute lymphocytic leukaemia at the ages of 2–4 years. Two of the siblings were twins probably binovular Genetic mechanisms in the aetiology of acute leukaemia are discussed and the pertinent literature is briefly reviewed.

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Fig. 1. External aspect of the hemangioma of the spleen (after sectioning).

Fig. 2. Microscopic appearance of the tumour X40 (hematoxylin eosin stain).

perform the slightest traumatic procedure such as a venipuncture, was followed by continuous bleeding and by the formation of extensive echymoses at the site of the prick.

In the beginning, we administered prednisone, 2 mg/kg of body weight. This dose was later increased to 4 mg/kg of body weight. At the same time, the patient was transfused with fresh blood and fibrinogen. Nevertheless, in spite of the above treatment, there was no change in either clinical condition or hematological findings. As the patient's condition was deteriorating, we decided to carry out splenectomy. At the time of the operation, the patient had been in hospital for three months. After removal, the spleen was sent for pathological examination and the report was as follows:

Pathology. The spleen was moderately enlarged; it weighed approximately 320 gm and measured 15 × 12 × 3 cm. The medial third of its long axis was occupied throughout its external aspect by a nodular tumour measuring up to 7 cm in greatest diameter. On section, the tumour was hardly discernible. It was of the same consistency and colour as the surrounding splenic tissue. The pulp mass was relatively homogenous, dark red, with indistinct follicles.

Microscopically the tumour showed an angiomatous structure, consisting partly of large sinusoidal spaces packed with red cells, and partly of smaller vascular channels, with a visible lumen. These vascular spaces were lined with flattened endothelium of the splenic pulp; many such lining cells in the angiomatous areas contained free iron pigment.

No lymphoid follicles were present within the nodules. The surrounding splenic tissue was compressed and the follicles immediately adjacent to the tumour were distorted. Some evidence of hemopoiesis was noted in the surrounding tissue.

Post-operative course. Following splenectomy the clinical condition of the patient improved dramatically and the hemorrhagic phenomena disappeared completely. The hematological investigations, immediately after the operation were as follows: The platelet count was 400,000 per cu.mm, the one stage prothrombin time 85%, and the

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Giant Hemangioma of the Spleen with Thrombocytopenia and Fibrinogen Deficiency

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Thrombocytopenic purpura as a complication of a giant hemangioma was first described by Kasabach & Merritt in 1940 [6] Since then nearly sixty similar cases have been published in the world literature In most of these the hemangioma was cutaneous, whereas in only a few the tumour involved the viscera [8]

In this paper we report a case in which a giant hemangioma of the spleen was associated with thrombocytopenia and fibrinogen deficiency

Case Report

X. A a male eight months of age was admitted to the children's hospital "Aglaia Kyriakou" with a 15 days history of purpuric lesions on the face trunk and extremities, epistaxis and hemorrhagic manifestations from the gums. He was born to a 28-year-old female, with a history of one previous normal pregnancy and one miscarriage which occurred during the fourth month of gestation. The pregnancy and delivery were uneventful The birth weight was 3 0 kg There was no history of hemorrhagic disorder in the family The neonatal period was normal and the child did well until the onset of the present illness.

Physical examination on admission He was an unusually pale infant, weighing 9 4 kg His body was covered by extensive purpuric lesions. His blood pressure was 80 mm Hg systolic over 55 mm Hg, diastolic and his pulse rate 110 per min, regular The liver was smooth and palpable 4 cm below the right costal margin, and the spleen, smooth and hard, was palpable 7 cm below the left costal margin

From the other systems: n.a.d.

Laboratory data Hb ranged between 6.3 gm/100 ml and 9.3 gm/100 ml; the leucocyte and differential counts were within normal limits.

The sedimentation rate was 2 mm in one hour The platelet count ranged between 25 000–60,000 per cu.mm. The plasma fibrinogen level was 50 mg/100 ml on three occasions. The one stage prothrombin time was between 15% and 30%. The clot retraction was nil after 4 hours and very little after 24 hours. The bone marrow was normal. The liver function tests were all within normal limits, the blood urea was 38 mg %

Radiological examinations X rays of the skull, chest and long bones were normal, and so was an intravenous pyelogram.

A barium enema showed that the left part of the transverse colon was displaced downwards and to the right; it was pressed by a mass, occupying the left upper side of the abdominal cavity X rays of the abdomen, taken during a barium meal with simultaneous injection of air into the peritoneal cavity showed the stomach to be displaced to the right by a big spleen

Course of Disease The hemorrhagic tendency was so severe that any attempt to

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plasma fibrinogen level 200 mg/100 ml. The patient was discharged in excellent condition on the tenth day after splenectomy. The above investigations, repeated two months later, yielded the same results.

Discussion

Because of the location of the hemangioma, this case presented as a difficult diagnostic problem. The diagnosis of idiopathic thrombocytopenic purpura was considered very unlikely in view of the greatly enlarged spleen. Both thrombocytopenia and fibrinogen deficiency appeared to be related to the hemangioma of the spleen, since both subsided after splenectomy.

We were very hesitant about the advisability of splenectomy because of the young age of the patient, the severity of his condition and the fact that his illness was very recent. However, removal of the spleen proved to be literally lifesaving.

This case is interesting because (*a*) hemangiomata rarely develop in the spleen and (*b*) the hemangioma in the spleen was associated not only with thrombocytopenia but also with fibrinogen deficiency. Appropriate investigations to clarify whether other factors in the mechanisms of blood clotting were also deficient were not carried out.

The mechanism by which hemangiomata cause thrombocytopenia is not clear. It was suggested by some authors that it results from decreased platelet production in the bone marrow [10]. Nevertheless, in most of the published cases, including *ours*, the number and the maturation of megacaryocytes in the bone marrow was found to be normal [4]. It is generally accepted that the platelets are destroyed after sequestration within the extensive vascular bed of the hemangioma. This is corroborated by the findings of Kontras *et al.* [7] and Brizel & Raccuglia [3]: following the transfusion of platelets labeled with chromium 51 these authors found increased radioactivity over hemangiomata causing thrombocytopenia. It should be noted, however, that in similar cases Petit [9], Blix & Aas [2] were unable to demonstrate increased radioactivity over the site of the hemangioma.

The associated fibrinogen deficiency in our case, as in other published cases, is difficult to explain. According to Beller & Ruhrmann [1], fibrinogen, together with platelets, is consumed in the process of *hemostasis within the tumour*. Alternatively, fibrinogen deficiency may result from repeated thrombotic episodes occurring in the vascular bed of the tumour; these may set off various fibrinolytic mechanisms [5].

Summary

A case of giant splenic hemangioma associated with thrombocytopenia and fibrinogen deficiency is described. The case presented clinically with severe bleeding and splenomegaly. Treatment with prednisone and transfusions of fresh blood and fibrinogen was unsuccessful in controlling the hemorrhage. Following splenectomy, the patient improved considerably, the bleeding tendency disappeared and the blood findings became normal. The relationship between giant hemangiomata, either visceral or cutaneous, and the disturbed mechanisms of blood clotting is discussed.

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